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SYSTEMIC BLASTOMYCOSIS

A REPORT OF ITS PATHOLOGICAL, BACTERIOLOGICAL AND CLINICAL FEATURES *

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The object of this report is so to relate the observations made in connection with a number of cases of systemic blastomycosis that a better understanding may obtain of the disease not only in this locality, where clinicians are already quite familiar with it, but also in places where it has been encountered but rarely or not at all.

Two summaries of the literature have already been made, that by Hektoen[1] dealing with thirteen cases, and the one by Montgomery and Ormsby[2] with twenty-two.

The second of these reviews contains brief accounts of the illnesses of four patients in this series and the post-mortem examinations on the bodies of two of them. The other two patients have since died and we are able to add the more detailed clinical records and the final results of the studies of material from two additional post-mortem examinations.

* Under the title "Medical and Surgical Reports of the Cook County Hospital for the Six Months Ending July 1, 1890," the first report containing scientific articles from this institution was published; it was edited by Louis J. Mitchell, M.D. A second report also edited by Dr. Mitchell with a similar title covered the succeeding six months. The third scientific report was entitled "Cook County Hospital Reports, 1906." It was compiled and edited by a committee of the attending staff and contained material which for the most part had been published elsewhere. The fourth and last report of this character was published in 1910. Like the third it bore the title "Cook County Hospital Reports." It was edited by a committee with Dr. E. R. LeCount as chairman. None of the articles in it had or have since been published elsewhere. Fifteen hundred copies of this report were printed bound in black cloth. Only three are at present known to be in existence. The remainder disappeared about the time there was a change in the board of commissioners of Cook County as well as a considerable change in the political composition of this board. What became of these reports is not definitely known. According to rumors they were burned by mistake. It has been thought best to reproduce the articles on blastomycosis which occupy 160 of the 196 pages in the original volume, since the observations they contain regarding this relatively rare disease would otherwise be lost or escape notice entirely.

1. Hektoen, Ludwig: Systemic Blastomycosis and Coccidioidal Granuloma, Jour. Am. Med. Assn., 1907, xlix, 1071; Chiari's Festschrift.

2. Montgomery, F. H., and Ormsby, O. S.: Systemic Blastomycosis, THE ARCHIVES INT. MED., 1908, ii, 1.

On account of the involvement of the bones, Dr. E. W. Ryerson[3] has considered the clinical and pathological relations of such changes to diseases for which it might be mistaken and utilized the observations made in connection with two cases of this series. To these five cases which have been but partially reported, there are added the hitherto unpublished observations on six additional cases, making the total number reported twenty-nine. I know of seven other instances of systemic blastomycosis, some of which will undoubtedly be published in the near future; six of these concern patients in Chicago or the immediately surrounding country. Of the twenty-nine cases reported, fourteen have concerned patients in Cook County Hospital, and of these eleven have occurred in the last two years. The total, thirty-six, represents an increase of over 200 per cent. during the last two years, and this without doubt is due to the great familiarity of physicians, especially the better clinicians, with the manifestations of the disease.

There are good reasons, as others have pointed out, for believing that the disease is frequently mistaken for tuberculosis; and judging from a number of the clinical histories in this series, it is evident that such errors are still likely to occur even here where the condition is perhaps best known.

The disease seems to be one of early life, as two-thirds of the patients have been under the age of 34, the youngest 17, the oldest 58 years of age; all but two occurred in men. The occupation in nearly every instance was one involving hard manual labor and considerable exposure. Heredity seems to have no influence, and no definite instance of contagion has been established. When this seems to have occurred, the exposure of all affected to a common case must be remembered. The majority of the patients have been foreigners, especially Poles and Italians, but no special nativity predilection has been noticed. Nearly all were poor and lived in unhygienic environment. Injury seems to have been a predisposing factor in several instances, either by affording opportunity for direct inoculation (see Cases 3 and 12 in the accompanying bibliography) or producing a region of lowered resistance for the development of the infection already existent (Cases 8 and 23).

The cause of this disease is now generally recognized to be a mold which, because of the budding form of the organism in the tissues, has been called blastomyces.

The reasons for considering the blastomyces as the cause of blastomycosis are, briefly, its presence in all the new or recent lesions, the readiness with which it is obtained from such lesions in pure culture, and the experiments on animals which demonstrate its pathogenicity. The organism has been recovered from the blood and is present in the pus of

3. Ryerson, E. W.: Am. Jour. Orthop. Surg., 1908, vi, No. 1.

unopened and discharging abscesses, quite regularly present in the sputum and sometimes demonstrated in the urine or feces.

Numerous descriptions of the organism, its cultural peculiarities and variations in morphology have been published.[4]

Some confusion still exists regarding the classification of blastomycetes and especially in regard to the significance of variations observed during the cultivation of different strains. Differences were first noticed in the study of organisms obtained from the cutaneous lesions of blastomycotic dermatitis, and Ricketts, in comparing the characteristics of seventeen organisms, six under his personal observation, found variations in their manner of growth sufficiently constant and distinct to allow of a classification into three morphological types, namely, blastomycetoid, oidium-like and hyphomycetoid.

The identity of the organism causing these cutaneous lesions and those found in the systemic infections was at first questioned, but as cases of the latter became more numerous, their identity was generally recognized. It was then ascertained that the variations were not sufficiently constant to allow of a separation into distinct types. Hamburger,[4] in a recent comparative study of four strains of blastomycetes obtained from patients with systemic infection, found one which differed somewhat from the other three, but not sufficiently to prevent the conclusion that the organisms were identical. Still more recently Montgomery and Ormsby have asserted that all the morphological types hitherto described have been observed at different times in the same strain. Many of the studies dealing with these matters have extended over rather limited periods of time and included comparatively few strains. We have studied altogether eleven strains: eight from the cases here reported (Cases 19 to 26) and three others, to the source of which reference will be made. The observations extended over a period varying in the individual strains from two to twenty months. In all instances the organisms were obtained in pure culture from the pus aspirated from abscesses, and similar organisms were also obtained in cultures from the sputum in most cases. They were also obtained from the blood of one patient (Case 19) and from the eye, pericardium and pleura in another (Case 20). A number of different cultures as to source were therefore obtained from each patient; and as they possessed no differences (except in Case 19) only one or two from each patient were used in the comparative study.[5]

4. Ricketts, H. T.: Jour. Med. Research, 1901, vi, No. 3; Montgomery, F. H.: A Brief Summary of the Clinical, Pathologic and Bacteriologic Features of Cutaneous Blastomycosis (Blastomycetic Dermatitis, of Gilchrist), Jour. Am. Med. Assn., 1902, xxxviii, 1487; Hamburger, W. M., Jour. Infect. Dis., 1907, iv, 201.

5. The organisms will be designated according to the case from which they were obtained.

As may be presumed, the morphological and cultural details of these different strains of organisms presented marked similarities, and in order to prevent repetition of details one general description will be given with the variations noted.

The organisms in the tissues, discharges and pus corresponded with those described in previous reports. They appeared in pairs or clumps as round or oval bodies, and budding was a common feature (Fig. 1).[6] The size usually varied, those about 20 microns in diameter being the most frequent, although larger forms (from 25 to 30 microns) were not uncommon, and innumerable smaller forms (from 3 to 5 microns)

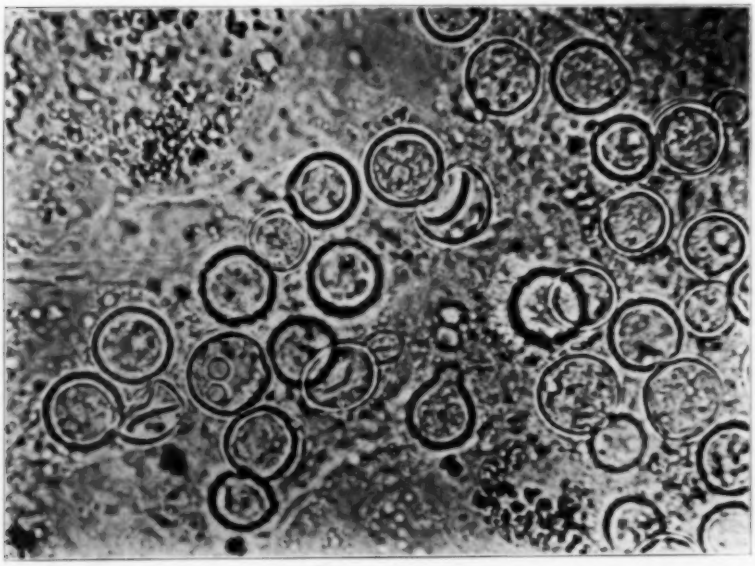

Fig. 1.—Specimens of pus containing blastomycetes mounted in a solution of potassium hydroxid. Note the round and budding forms, the refractile capsule and the vacuoles and granules in the center. (Courtesy of Dr. O. S. Ormsby.)

were sometimes found. Ordinarily the outer refractile capsule and clear central portions could be recognized. The capsule was homogeneous and double-contoured, and varied in thickness, being thinner in the smaller and younger forms. It was occasionally absent, especially in the organ-

6. The illustrations presented in this and the following articles on blastomycosis were (except where noted) prepared by me and formed the basis of a research exhibit presented at the 1908 session of the American Medical Association. The roentgenograms were prepared by Dr. H. E. Potter, roentgenographer to the Cook County Hospital, and are included in an article on "Radiographic Appearances of Pulmonary and Osseous Blastomycosis," published in the American Quarterly of Roentgenology, May, 1910.

isms of old foci. In sections of a bone-abscess a thick or adventitious capsule described by other writers was found. The capsule rarely stained by the ordinary methods. The central portion in the fresh condition was usually clear, and stained more or less granular, taking basic stains and coloring light blue with hematoxylin, and red or violet with polychrome methylene-blue. Occasionally the central portion stained intensely, and when the capsule was absent or indistinct, such organisms resembled small lymphocytes. In other organisms it remained unstained or presented the same color as the surrounding tissue. In the fixed and stained as well as the unstained organisms, one or more vacuoles may be present, but the most common feature in the former was the presence of small spherical basophilic granules, usually from three to ten in number. Although quite regularly arranged, their distribution in the cell cannot be said to be characteristic. They were often found in the budding forms and in some instances appeared to be contained entirely in the bud. The association of these granules with spore-formation has been suggested by a number of writers on this subject. According to most observers, proliferation in tissue occurs by budding. Hyphae have not been found in the tissues, and sporulation has been suggested in but one instance (Case 8), the extremely small size of the organisms and occurrence in clusters being the chief reason given. In old cultures a vacuolization occurs which strongly resembles sporulation.[7]

The blastomycetes grow readily on ordinary mediums. No difficulty was experienced in obtaining growths on sterile moist bread, paper, cardboard, cotton, sawdust, fruit and vegetables. Isolation from other organisms can usually be accomplished by making a thin stroke on a dry agar surface, the tendency of the blastomycetes to extend over the surface

7. In our studies, a process thought to be endosporulation was observed in one instance. In an agar-slant culture of a strain obtained from Case 19, sixteen months old at the time, a contamination occurred and the surface became covered with a slimy saprophytic growth. Examination of a smear before discarding disclosed the presence of a large number of round forms of blastomycetes scattered among the bacteria, which belong to the *Bacillus subtilis* group (Fig. 2). Budding and hyphal forms were absent. Bodies considered to be spores appeared in the organism as round clear objects which varied markedly in size and distribution (Fig. 3). Sometimes only one or two were present in a cell, but they usually occurred in large numbers, irregular in size. In some cases a fairly regular distribution was noted. The larger forms sometimes extruded from the cell, and in other instances the cell outline was lost in a zooglea-like mass of cluster of the smaller forms, similar to those observed in tissues. That these appearances were due to a reproductive rather than an involution process was assumed because of the innumerable small round forms present, the similarity, even to the refractile capsule, of the younger forms within the parent cell to those lying free in the neighborhood, and the absence of any other form of reproduction. The same process also was observed to a less extent in a subculture from the tube described above. It was impossible to isolate or obtain growths of the blastomycotic organisms in subsequent cultures, owing probably to the innumerable bacteria which were present.

making it possible to obtain pure subcultures. In a few instances this was accomplished by spreading the suspected pus, diluted with bouillon, over a large area of sterilized bread.

A proliferation by budding, such as occurred in the body, is at first observed on mediums, but sooner or later the production of hyphae and myceliums characteristic of the mold growths occurs. Budding is favored by moisture and thermostat temperature, the other methods of growth by

Fig. 2.—A preparation made from a blastomycetic culture which had become contaminated with *B. subtilis*. The innumerable small round forms suggest endosporulation.

room temperature, dryness of the mediums and transplantation. The time required for the appearance of the hyphal form varies somewhat. In a few instances hyphae were noted in the first cultures made from the pus and kept at room temperature; in others the budding persisted for some time.

The gross appearances of the cultures depend largely, as might be expected, on the method of multiplication, and many of the variations

reported are undoubtedly due to the degree of transition from budding to other forms of growth present at the time of observation. As mycelial growth becomes more marked the budding forms are less numerous and often difficult to demonstrate; but even after months of growth of the mycelial type on agar, a few budding forms may be found in the deeper parts of the cultures.

The pure budding form (blastomycetoid type) may occur primarily in cultures from pus or may appear later under certain conditions as a

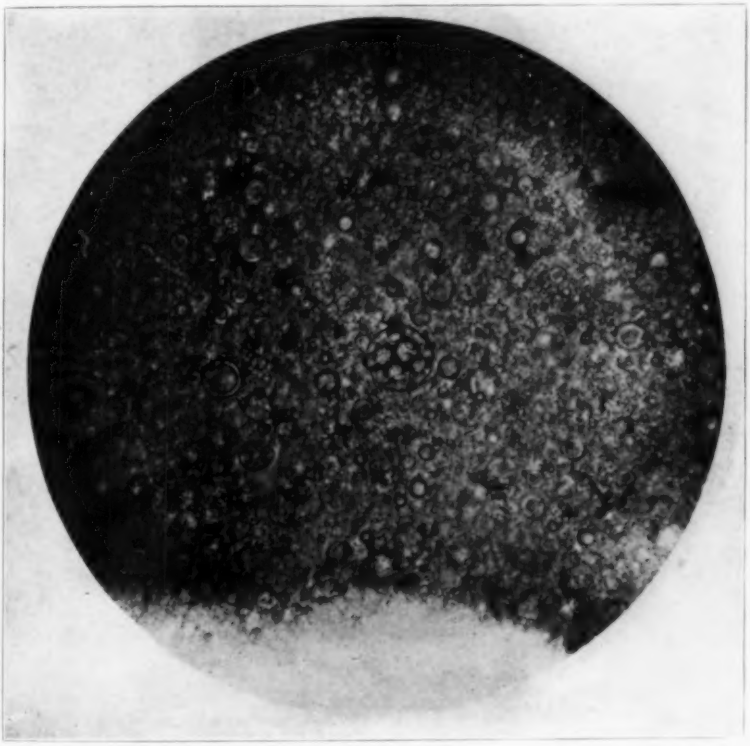

Fig. 3.—Endosporulation? Higher magnification. The innumerable small round forms are more plainly seen.

reversion from the mycelial form. The colonies on agar were at first small and round and presented a pasty appearance. They varied in color from white to light yellow and were easily detached and broken up. Later as hyphae began to form, they assumed a waxy or porcelain-like appearance, became tough and adherent, and subsequently formed a surface membrane which in some tubes became nodular or rugose (Tubes *a* and *b*,

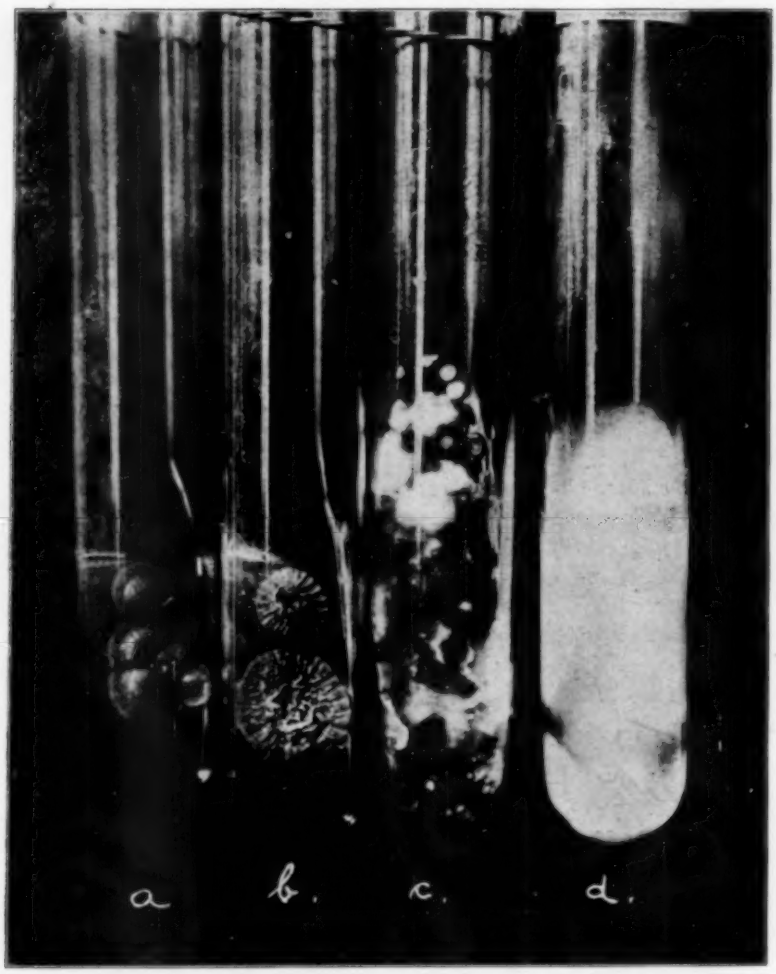

Fig. 4.—Cultures of blastomycetes, Type 1: (*a, b*) nodular and rugose appearance of colonies on glucose agar; (*c*) mixed forms — beginning formation of aerial hyphae causing white fluffy appearances; (*d*) characteristic white fluffy growth of the mycelium with aerial hyphae.

Fig. 5.—Cultures of blastomycetes Type 1, showing nodular, rugose and "bundle of worms" appearance.

Fig. 4), or assumed the "bundle of worms" appearance (Fig. 5). Subsequent cultures usually presented the characteristic mycelial growth (Tubes C, D, Fig. 4). It is of interest to note that such rugose or wrinkled surface membrane growths were more common during the fall and winter. Indeed, some of the strains which at room temperature during the summer grew abundant aerial hyphae, during the months of October and November grew these surface membranes which consisted principally of budding or short hyphal forms.

Single colonies of the mycelial type appeared as fine branching hyphae, radiating from a faint yellowish-white center. The hyphae grew into the mediums and also on and beneath the surface, increasing in number and extent until a membrane was produced. Viewed directly, such colonies appear as a moist fine, meshed or felted network of branching hyphae, having a slightly raised center. Viewed by transmitted light, the extent and manner of the growth of the refractile mycelium can easily be seen (Fig. 6). After longer growth the membrane may cover the surface and become very thick and adherent, the agar beneath often showing a brownish discoloration. In some cultures the hyphae may not become aerial, and proliferation occurs by the segmentation of the mycelium into spores. This corresponds to the oidium-like type of Rickett's classification. Later in the growth, however, or in the subsequent subcultures, the hyphae in the center of the separate colonies or on the surface of the diffuse growths become disengaged or raised from the surface and may bear lateral and terminal fruit-buds. This formation of aerial hyphae, giving the cultures the white, fluffy, mold-like appearance, occurred sooner or later in all the strains, and was for a time regarded as the final typical stage in the life of the organism (Tube D, Fig. 4). The aerial hyphae, at first short and thinly scattered over the surface, often become luxuriant, growing up the sides of the glass and sometimes filling the test-tube. In some cases aerial growth occurred in the first culture made from the pus. This form corresponds to the aerial or hyphomycetoid type in Rickett's classification. It will therefore be observed that the various forms described above, on which the classification of distinct morphological types was based, represent different stages in the life history of the organism. A gradual transition from the budding form (blastomycetoid) to the submerged and surface mycelial (oidium-like) growth, the hyphae of which later became aerial (hyphomycetoid), can be seen in any one strain, if observed for a sufficient length of time. These three forms, then, hereafter will be considered as variations of blastomycetes, Type 1, in contradistinction to Type 2, another form to be described, showing radical differences and representing, so far as has been observed, a possible final stage of growth or reversion type.

Glucose-lactose agar gave much more luxuriant growths than the plain agar. No differences could be observed in tubes of 0.6 per cent. acid, neutral and 0.6 per cent. alkaline reactions. Growths on potato, gelatin and serum agar showed no characteristic differences, except that on the latter, which contains glucose, the growth was more luxuriant and wrinkled surface membranes occurred more often.

Growths in bouillon inoculated with pus appear as fine sediment in the bottom of the tube, and in shaking can be seen to be finely granular. On examination, this consists of budding or short hyphal forms. Later, a number of round discrete mycelial tufts closely resembling thistle-down appear. In the test-tube these soon become confluent, forming a coherent mass, which can often be removed entire with the platinum wire. A single colony grown in the flask increased in size until it filled that part containing the medium, and retained its circular form. The older mycelium in the center of such large colonies undergoes a degeneration and becomes translucent, giving the growth a hollow appearance. When the mycelium reaches the top of the medium, a tough surface membrane is formed, on which aerial hyphae develop. Sometimes before the development of the latter the membrane sinks to the bottom, becomes brown and gelatinous, and finally disintegrates, while another may form on the surface. In subcultures, in which the transplanted material floats on the surface or remains adherent to the side of the glass, a surface membrane only may occur.

The form already mentioned as Type 2 appearing in subcultures of Type 1 was first obtained in a subculture on agar of an old bouillon growth of an organism from Case 22. In a rather diffuse growth of Type 1 a number of white small waxy colonies were observed and for a few days regarded as a contamination. When an attempt was made to remove them for examination, they were found to be very hard in consistency and quite adherent. The structure was mycelial in character and pure cultures were then obtained. The appearance of this mixed culture and also the first pure culture are shown in Figure 7. The character of this new type corresponded to the growth obtained from the blood in Case 19, and for this reason was considered to have some relation to Type 1. This type was afterward obtained from the cultures made from the pus in Cases 19, 20, 21, 22, 23, 25 and 26.

The time of appearance of the Type 2 is variable. It occurred immediately in cultures from the blood in Case 19, in five weeks in cultures (Type 1) from the pus in Case 25, and fifteen months in cultures from the pus in Case 18. Its occurrence seems to be favored by prolonged growth on liquid mediums and a gradual transition has been observed.

Fig. 6.—Blastomycetic cultures viewed by transmitted light: (*a*) Type 2; note the limited marginal growth of mycelium; (*b*, *c*) Type 1; submerged and surface mycelial forms whose manner of growth is more plainly shown.

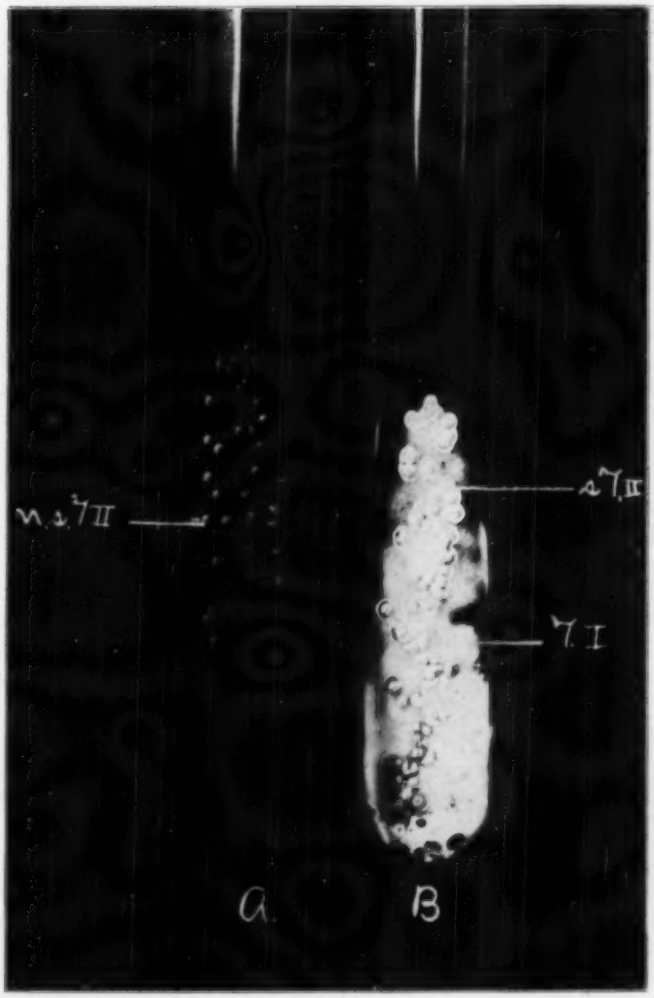

Fig. 7.—Cultures of blastomycetes obtained from pus: (*a*) non-sporulating form of Type 2 isolated form; (*b*) a culture of the usual Type 1 in which colonies of sporulating Type 2 (s T II) appeared.

On agar the colonies of Type 2 appear as round, glistening, opaque, white or yellowish growths, resembling closely those of staphylococci. They differ, however, in that they are tough and adherent. As the colonies become older they sink into the medium and the margins are depressed beneath the surface. Occasionally a cleft or circular opening appears in the center, giving a burst-bubble appearance. The next change observed in the same tube or in a subculture is a marginal growth of hyphae, which by transmitted light appears as a halo about the colonies (Tube A, Fig. 6).

With plenty of moisture at incubator temperature, the discrete colonies may attain a diameter of a centimeter or more, the surface then becoming moist, slightly granular and wrinkled. When the colonies become confluent a membrane is produced which, owing to the rapid central growth, becomes wrinkled or corrugated, similar to Type 1. The last, and so far as has been observed, the final stage, is the production of short hyphae bearing many small spores. The surface now presents a white powdered appearance (Fig. 8), although on glucose medium a gray has been noticed, and on several occasions a slight pink or red was observed. Glycerin medium, probably by preserving the moisture, seems to retard spore development. Reversion of Type 2 to Type 1 has not been observed. Type 2, then, so far as is known, represents the form finally assumed by the organisms after removal from the animal body, and is the form in which spore formation occurs to the greatest extent, resembling the natural molds in this respect. A minute portion of the spore form of Type 2 will produce innumerable colonies, whereas a considerable portion of the mycelium of Type 1 must be used to secure a growth. The possibility of obtaining the budding form by inoculation of animals with Type 2 is at present under investigation.

In cultures of Type 2 grown in bouillon the colonies are small, rarely attaining a diameter of more than a few millimeters. They usually remain discrete, and if they should become slightly coherent, separation readily occurs on shaking. In case any of the growths reach the surface a membrane also is formed, the surface of which assumes a white powdered appearance which is characteristic of the sporulating growths on agar. A distinct and characteristic musty odor is usually present.

Litmus Milk: The results of growths of either type on litmus milk were variable. In a few instances the milk became acid, but in the majority it was alkaline or unchanged. Coagulation occurred several times, but was not constant.

Fermentation Tubes: Both types of the organisms of the first five cases were tried with maltose lactose, dextrose and inulin bouillon, but no gas formation took place. All but two of them were tried later with dextrose and lactose bouillon with the same result.

The organisms resist drying for prolonged periods, growths having been occasionally obtained from dry cultures over eight months old. The presence of bacteria in the cultures seems, however, to inhibit the growth, and finally destroys the blastomycetes. The organisms are also readily killed by heat, 100 C. (212 F.), 1 per cent., dilution of liquor formaldehyd and chloretone, 0.8 per cent., and phenol (carbolic acid), 5 per cent. solutions. Sunlight and lack of moisture also inhibit the growth.

Morphology of Cultures: The morphology of blastomycetes Type 1 in cultures has been so well described and illustrated by other writers[8] that nothing of importance can here be added, and the structure of Type 2 is so minute that a detailed description is difficult to give. So far as has been observed, the mycelium corresponds in nearly all details to that of Type 1, except that it is very minute, the individual hyphae appearing as fine lines, with even the 1/12-inch lens. The spores appear very similar to cocci. Figure 9 shows fairly well the general appearance of the mycelium in contrast to that of Type 1 (Fig. 10, same magnification).

Experiments with animals to demonstrate the pathogenicity of the culture we isolated were not so successful as some reported by other observers. Dogs, rabbits, guinea-pigs, white and gray rats and white mice were used. The material inoculated consisted of pus aspirated from abscesses, and both fresh and old agar and bouillon cultures. The quantity varied from 1 to 7 c.c., and this was injected subcutaneously, intraperitoneally, intravenously and intratracheally. Death never was produced except when the cocci were present in the material inoculated. A number of white mice died apparently from the trauma of the injection. Subcutaneous inoculations usually produced abscesses, sometimes enormous in size, all of which healed spontaneously with or without rupture. Demonstration of the organisms in these abscesses and their cultivation was possible only during the first few days following inoculation. Injection into serous cavities or the veins produced a transient illness. Animals killed at varying periods after intravenous inoculation showed no microscopic systemic lesions. From agar-plates of the heart-blood of one rabbit killed two days after inoculation luxuriant colonies were obtained. I should conclude, therefore, that the lower animals are markedly resistant to blastomycotic infection in spite of its power to produce suppuration. It is possible that in the human being the resistance must be considerably diminished before infection takes place.

The obviously serious nature of the disease in man and the increase in the number of cases taken into the hospital naturally occasioned anxiety on the part of the attendants in regard to the possibility of contagion from the patient's sputum or the profuse purulent discharges, and the question of isolation arose. During the spring of 1908 a slight

8. Ricketts, H. T.: Jour. Med. Research, 1901, vi, No. 3.

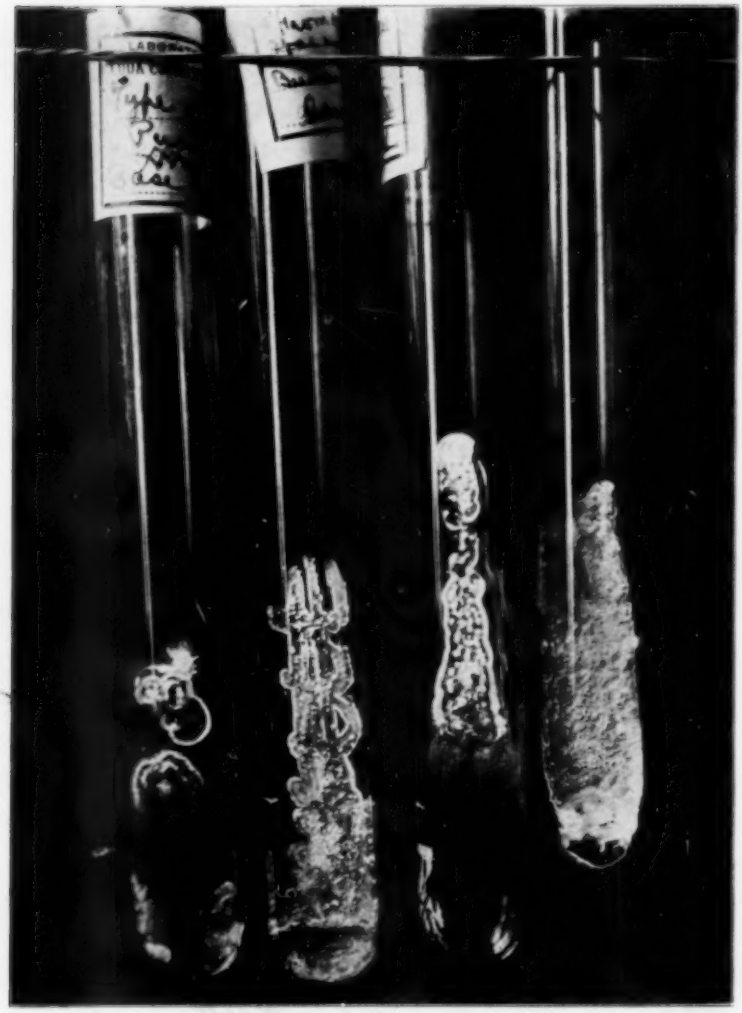

Fig. 8.—Cultures of blastomycetes Type 2. Growths of Type 2 are at first smooth and waxy. Later, spores are formed giving the surface a white powdered appearance.

nasopharyngeal infection was present among the hospital attendants. The throats of fifteen who had directly or indirectly been exposed to blastomycosis were examined. No organisms were found in the pharyngeal or bronchial mucus, nor were any cultures obtained. Strict isolation was not established, but reasonable precautions were observed. To our knowledge no one has been infected, and it is improbable that infection with the organism as it exists in the pus or sputum occurs except by direct inoculation. It may be advisable to mention at this point an incident which might have a bearing in the danger of handling the cultures.

Fig. 9.—Photomicrograph of mycelium from a culture of blastomycetes Type 2. It presents the same general structure but is much smaller than Type 1.

During the laboratory work a test-tube containing a bouillon culture of blastomycetes (Type 2—sporulating) from the blood of Case 19, was broken in the presence of another person and myself. The odor was very irritating, and it is not improbable that a number of the spores were inhaled. In spite of sprays and an antiseptic gargle, a pharyngitis and laryngitis developed in one of us. The other experienced a chill about six hours later, and a purulent bronchitis developed lasting for three days, associated with considerable fever. No organisms, however, were obtained in films or cultures made from the sputum.

The resemblance of growths in cultures of these organisms to those of natural molds, and the ease with which (like the latter) they could be grown on moist bread (Fig. 11), cotton and various forms of cloth and paper, led to an investigation of the home surroundings of several of the patients as well as the conditions prevailing in such places when the disease began. The results are especially noteworthy, since in nearly all the reported instances in which the onset of the disease could be

Fig. 10.—Photomicrograph of culture of blastomycetes Type 1. It shows plainly the budding and hyphal forms.

determined, it was learned that the first symptoms developed during the months when in this region great dampness and mold growth prevails.

One patient (Case 19) lived in a basement on Huron Street. At the time of investigation it was uninhabited and entrance could not be effected. Through a broken window, however, the rooms were seen to be very dark. The floor was laid directly on the earth, and a number of the boards were completely decayed. From the neighbors it was learned

that the family had very unhygienic habits, and that owing to lack of room the patient had often slept outside under the sidewalk. Another (Case 20) lived in South Chicago, also in a basement with a low ceiling and painted walls. The wooden floor was several feet below the level of

Fig. 11.—A loaf of bread three weeks after inoculation with blastomycetes Type 1. The mold has spread over the entire loaf.

the street, and the surrounding land was marshy and covered with pools of water. When examined (November) the rooms had been renovated and were in a fairly sanitary condition. The wife, however, stated that after the snow came and the ground was frozen, the floors were always

damp, and that this was increased by the condensed steam trickling down the walls; also that the bed-clothes became so moldy that each spring they were forced to burn the mattresses. A third patient (Case 21) lived on the second floor of a three-story building. The basement, in which the closets of the tenants were situated, was dark, requiring the use of candles in the daytime. The floor of this basement was partially flooded with water, which was escaping from the sewer-pipes. The planks covering the floor were in various stages of decomposition, and presented much mold growth.

The fourth patient (Case 22) for six months prior to the onset of his illness had lived in a cabin-boat while engaged in dredging. A fifth

Fig. 12.—A flash-light photograph of a basement in which one of the patients slept during the winter he was infected. His bed was made of old carpets on a pile of sand near this board wall, which was banked with earth on the outside. For several inches above the point where the boards (*bo*) entered the earth (*ea*), a brown fungous growth (*mo*) was present. Above this, for some distance on the board the fungus was dry and the surface was covered with spores, giving it a white powdered appearance (*sp*). The growth was most luxuriant during fall, winter and spring months.

patient (Case 23), during the winter he was infected, slept in a basement located in the "Ghetto" on the West Side of Chicago. It was low, dark and poorly ventilated. The wooden walls were backed with earth, quite moist in places and covered with a brown fungus growth. Where the wood was dry a white powder-like deposit was present (Fig. 12). The

Fig. 13.—Fungus growth on a piece of wood removed from the basement illustrated in Figure 12.

patient slept on a pile of dirt near this wall, and his coverings consisted of several carpets which were also moldy. Several pieces of the decayed boards were removed and taken to the laboratory. The general appearance of the fungus growth was not unlike that of brown plush (Fig. 13). On drying the surface became covered with a white, powder-like deposit (Fig. 14). The same changes took place on the walls of the basement during dry weather. This powder when inoculated on agar gave pure cultures of a mold which differs in only a few respects from the blastomycetes, Type 2, to be described presently. Inoculations from the bouillon in which this fungus has been triturated also gave a large number of colonies of this type, and a few of another type. A low-power view of a section of the wood and attached fungus is shown in Figure 15. The general mycelial structure in which compartments of spores exist can be made out as the magnification is increased, and two varieties of circular bodies can be recognized[9] (Fig. 16).

A sixth patient lived near the lake in South Chicago, on the second floor of a two-story frame house built from 3 to 5 feet below the street-level and covered with water during the winter and spring. One small cooking-stove supplied the heat in winter for the rooms occupied by sixteen men. When examined in August the room, which had painted ceilings, was dry and well aired. During the drought of July and August, 1908, the dirt floor of this basement was still wet, and white mold spores were found on the timbers.[10]

The residence of a seventh patient (Case 25) could not be located. It was learned, however, that he had lived in the Croatian colony in South Chicago for three months. The dwellings there are old frame houses built on ground so low that the first floor is 3 feet below the street level.

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9. The first is a clear, round, translucent body, and is the variety which is most abundant. They are produced by segmentation of the hyphae, and probably constitute the spore form. The second variety is larger and usually dark brown. A few of these can be seen in the surface mycelium, but they are most abundant in the substance of the wood. Some appear to be formed in the hyphae, and in other places the hyphae seem to originate from them. Except in color they resemble closely the blastomycetes found in pus. In Figure 17 the double contoured round and budding forms can be seen distinctly. A teased specimen of the surface mycelium shows branching and segmentation similar to that observed in cultures of blastomycetes (Fig. 18). The first-mentioned cultures differ only from blastomycetes in that the growth is more rapid and luxuriant and that a red color appears in the growths on glycerin-agar, although a slight pink has been observed in the growths of Type 2 obtained from the blood-cultures. The second variety obtained from the wood resembles Type 1 in appearance, but it bears abundant elongated or cigar-shaped spores. In later cultures these spores become round. Photographs of these cultures are seen in Figure 19. Note resemblance to cultures of blastomycetes (Figs. 4 and 8).

10. Some of the material was removed to the laboratory, and nearly pure cultures of a mold resembling those already mentioned were obtained.

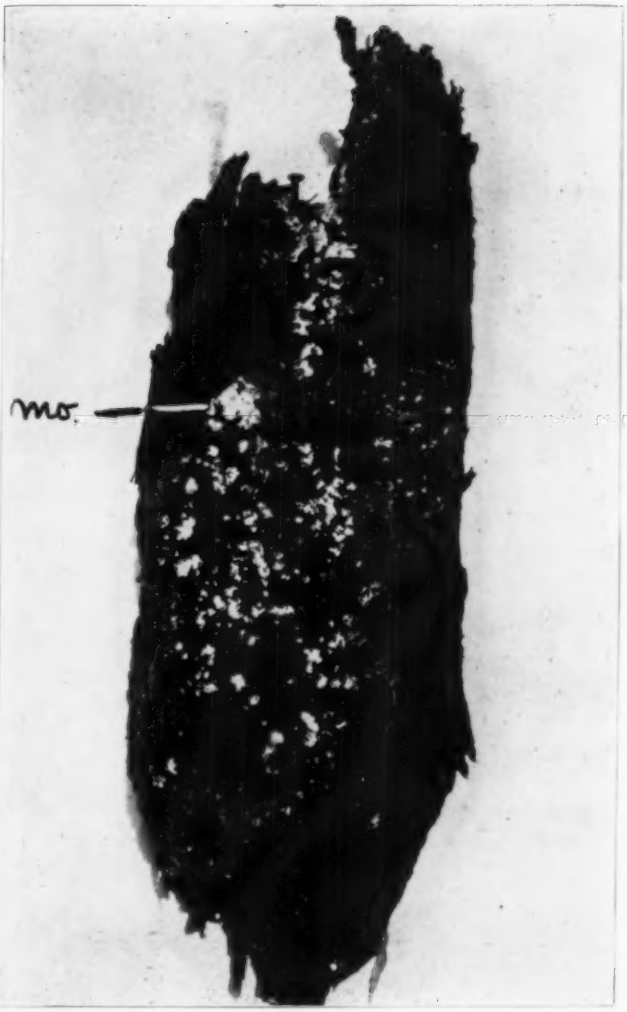

Fig. 14.—Another piece of wood from the same basement. The photograph was taken several weeks after it was removed to the laboratory and shows the numerous areas of white fluffy mold (*mo*) which appeared.

An eighth patient (Case 26) lived on the North Side, on the second floor of a two-story frame building; the first floor was used as the wash-room of a steam laundry in which the patient worked. The floors were old and necessarily damp. No molds were discovered in this room, but in an adjacent closet a profuse mold growth was found on the floor. Immediately under the window of the bedroom was a small shed used as a storeroom, and often frequented by the patient. The floor at the time of investigation (July) was covered with litter which was damp and moldy. The occupants stated that during the fall, winter and spring,

Fig. 15.—A low-power field of a section of the fungus illustrated in Figures 23 and 24: (*wo*) wood fibers; (*hy*) mycelium made up of hyphae enclosing (*sc*) spore compartments; in the latter are a large number of (*sp*) spores.

water was always present under the floor and could be forced up between the cracks of the boards by the weight of the body. Two barrels of decaying manure stood just outside the door.[11] No mold could be found in the living-rooms upstairs. It was learned, however, that during the winter the walls were always wet from the condensed steam of the laundry

11. It is noteworthy to mention that one of Dr. Ormsby's patients at the time of infection slept in a room, the windows of which were located just above a manure-pile.

below. The bedroom was so small that there was room only for the bed. The only window was the one mentioned as located just above the shed and manure barrels. Specimens of moldy wood and leather from the shed and closet were taken to the laboratory and cultures obtained which resembled those already described.

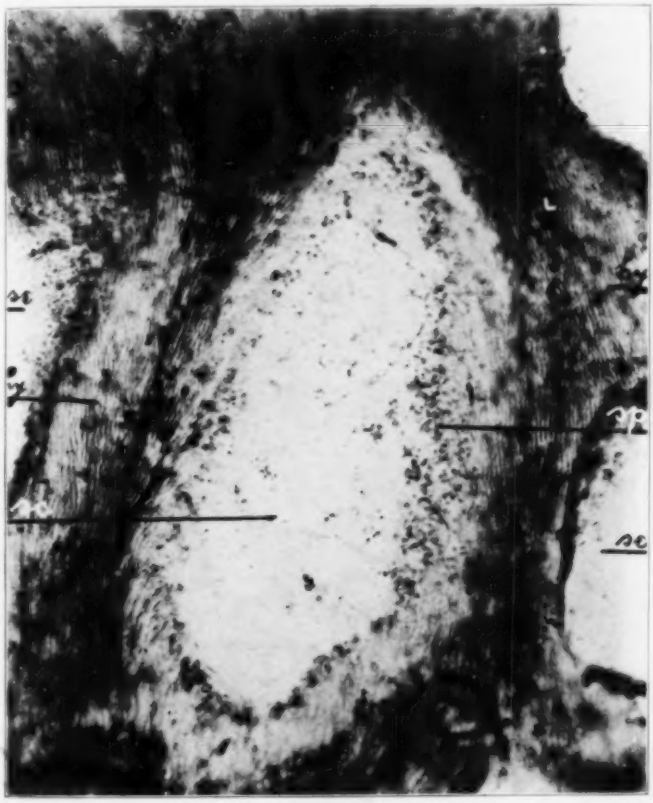

Fig. 16.—A higher magnification of the wood mold showing more plainly the (*hy*) branching segmented hyphae, (*sc*) spore compartments and (*sp*) spores.

The patient with cutaneous blastomycosis, mentioned subsequently, lived in a house the walls of which were constantly damp during wet weather. The roof leaked to such an extent that it was necessary to provide vessels to catch the water. He did not remember having seen any mold in the house, but states that musty or moldy odor was always present.

In view of the uncertainty expressed in botanical literature as to the closely related organisms, and because no one has undertaken to determine the final place the blastomycetes shall occupy in the systemic mycology, it is hardly pertinent to more than suggest that like other molds these organisms may possess a native habitat in such insanitary dwellings as those from which these patients came. It would also be hazardous to do more than suggest an identity between the molds grown from decaying boards and walls in these dwellings and the blastomycetes, although in many respects points of similarity were demonstrated, such as morphology, cultural reaction, pathogenicity and vaccine reaction.[12]

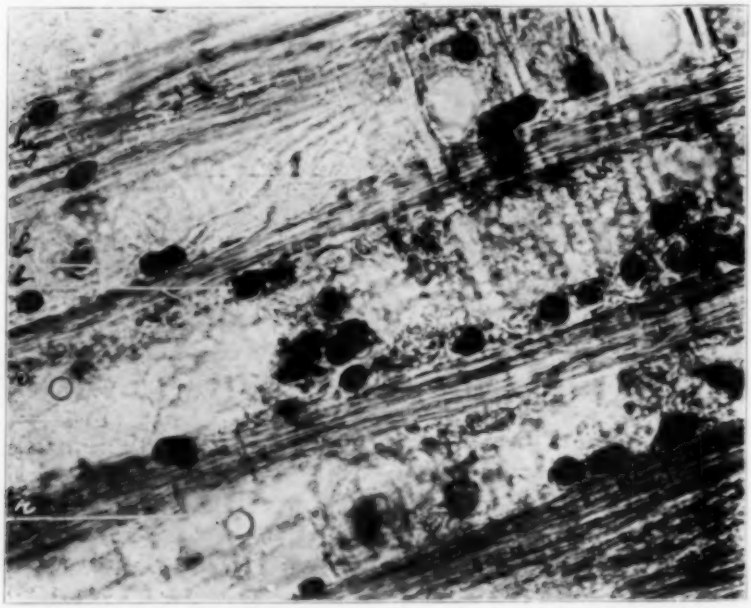

Fig. 17.—Photomicrograph of the wood just underneath the fungus, showing round (*r*) and budding (*b*) forms of organisms with refractile outlines. Segmenting hyphae (*hy*) can be seen running parallel to the wood fibers.

The suggestion of infection from these natural sources by inhalation is perhaps justified to a certain extent in that it is generally held at present from both the clinical and pathological evidence that the respiratory tract is the atrium of infection in systemic blastomycosis. In at least fourteen of the cases reported the first symptoms were referable to the lungs, and of eleven necropsies in these cases, nine presented old

12. See Case 6, vaccine therapy, also in a subsequent discussion in this article.

bronchopneumonic lesions. It is also possible that the subcutaneous abscesses or cutaneous lesions marking the onset in other patients were due to unrecognized pulmonary lesions with metastases in the skin and elsewhere. In man no very good evidence of infection of the intestinal tract has been obtained. In four cases of this series the Peyer's patches were reticulated and pigmented, and in two cases the mesenteric lymph-nodes were enlarged. In another case (Case 7) peculiar nodes were found in the colon and regarded by the authors as blastomycotic; organisms,

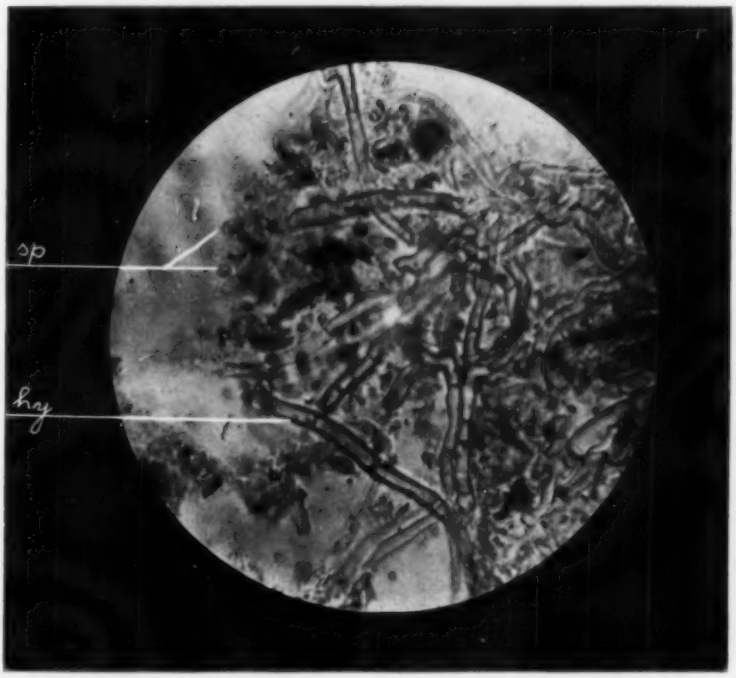

Fig. 18.—A teased bit of mycelium from the wood mold showing the segmentation of the branching hyphae (*hy*) and the round spores (*sp*).

however, have not been demonstrated in either the bowel or mesenteric lymph-nodes.

As for infection of the skin, such a large number of cases of cutaneous blastomycosis have been reported that this condition is no longer regarded as uncommon. In some of these it seems quite evident that the infection followed some form of traumatism. In only three instances, however, has it been clearly established that systemic infection followed, and in these, the cutaneous lesions existed for from seven to twelve years,

respectively, before symptoms of systemic blastomycosis were manifested. In once case (Case 12) the infection occurred several months after cutting the foot on a clam-shell. That direct inoculation does occur was established in two of our cases in which new superficial lesions developed in the abrasions resulting from scratching. Blastomycetes were found in the detritus under the finger-nails of these patients and undoubtedly had origin from preexisting ulcers which the patients persisted in scratching.

Pathology: The skin and lungs have already been mentioned as constituting the principal atria of infection. The spread of the organisms from these points and the resulting pathological conditions depend very much on the resistance of the individual and the location of the primary lesion.

Dissemination of organisms from cutaneous lesions does not seem to have occurred very often. These lesions have considerable tendency to spread by contiguity of tissue, but invasion of adjacent lymph-nodes is not common, and in only a few instances have the organisms entered the blood-stream, producing metastatic lesions in the lung and systemic infection. In two cases this process seems to have followed directly the curettement of the cutaneous lesions.

Primary infection of the lungs, as pointed out before, appears to occur first in the bronchi, to be followed by the development of areas of bronchopneumonia in the neighborhood. Further lymphatic spread is possibly responsible for the pleuritis, pericarditis and mediastinal lymphadenitis which have been noted. From these lesions in the lung, organisms may enter the blood and become distributed throughout the system with the production of multiple metastatic foci, which in turn may give rise to further dissemination by the blood route and reinfection of the lung. The repetition of these processes may thus constitute a vicious circle and afford ample explanation for the numerous metastatic lesions characteristic of this disease. The skin, muscles, subcutaneous tissues and the bones of nearly every part of the body have been involved, and all of the important viscera have presented more or less evidence of infection.

The variation in the reaction of the tissues to the presence of the organisms noted in a single case are most remarkable. Blastomycetes in considerable numbers were not uncommonly found associated with no histological change whatever. In other instances slight necrosis was the only alteration noted.

The majority of the infected areas, however, presented round-cell infiltration, either alone or associated with giant-cells, polymorphonuclear leukocytes, or both. In some tissues, especially in the viscera, in which the lesions were small, definite nodules were found and closely

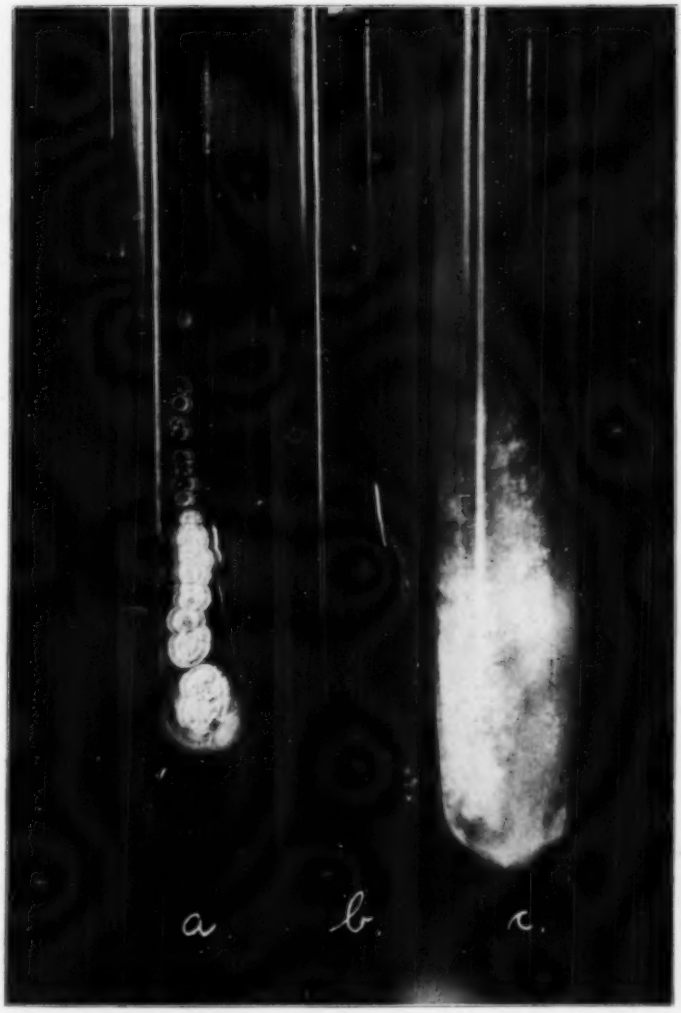

Fig. 19.—Cultures made from the wood mold gave a large number of colonies (*a*, *b*) closely resembling those of blastomycetes Type 2 obtained from blood and pus. A few colonies resembling blastomycetes Type 1 were also obtained and shown in tube (*c*); (*a*) and (*b*) are the same, except that the former is the older culture and sporulation has occurred, giving it a white powdered appearance.

resembled those found in tuberculosis except that central necrosis was less marked. Other nodules contained many polymorphonuclear cells constituting small abscesses. These were found either discrete or confluent, the latter being separated by blood-vessels and bands of compressed tissues. Some were very small, occupying an area equal in diameter to one-half of a high-power field. The larger abscesses were often surrounded by a distinct wall of granulation-tissue. Giant-cells usually were present, often in considerable numbers. Their absence in a few instances was especially noted. They were usually of the Langerhans type, but were rarely as typical as those found in tuberculosis. In some cases heal-

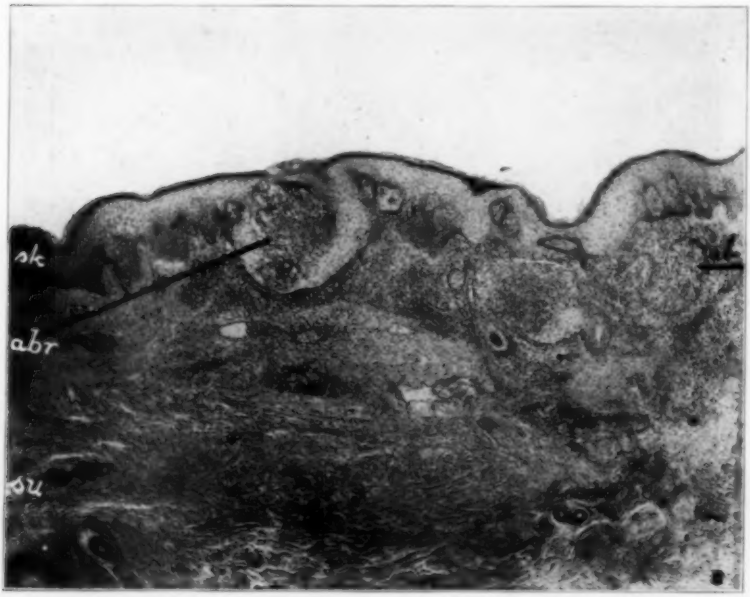

Fig. 20.—A section showing blastomycotic abscesses in the skin and subcutaneous tissue: (*sk*) skin, the epithelial layer of which has been involved secondary to (*ab*) the subcutaneous abscesses; (*abr*) an abscess about to rupture; typical cutaneous lesions often develop at these sites.

ing of the infected areas occurs and is often associated with marked fibrosis, especially in the skin, lungs and pleura.

The changes most characteristic of blastomycosis are the cutaneous ulcerations, the deep and superficial abscesses, and the often tubercle-like nodules in the viscera. Some of these lesions deserve special mention.

The infections in the skin may appear as pustules, subcutaneous abscesses or local ulcerations (Figs. 20 and 21). The pustules are usually multiple and may occur successively or in crops. The ulcers

may occur primarily as such or develop in the site of the ruptured abscesses. In cases of the latter, the ulcer produced is usually surrounded by an areola of inflammation; the margins are slightly raised and irregular, and the base is soft and covered with granulation-tissue, which may become fungoid and approach the surface, later assuming a papillomatous appearance, which is more or less characteristic of the lesions of chronic blastomycosis of the skin (Fig. 22).

The abscesses may be superficial or deep and have origin in the skin, subcutaneous tissues, lymph-nodes, muscles, bones, nervous tissues and viscera. Their size is most variable, ranging from very minute areas to

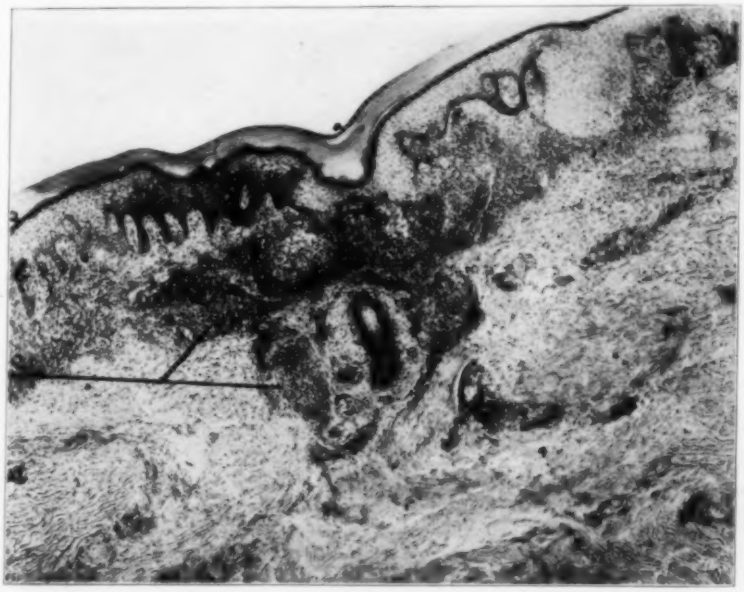

Fig. 21.—Photomicrograph of a section of subcutaneous abscess: (*a*) stratum corneum; (*b*) papillary layer which is being invaded by (*c*) the abscesses containing large number of blastomycetes; infection here occurred from the blood; (*d*) subcutaneous tissue.

enormous cavities containing a quart or more of pus. Those having origin in the deeper tissues are more or less hard at first, but fluctuation develops sooner or later. Some are associated with pain and the signs of inflammation, whereas others are discovered by the patient accidentally. Spontaneous healing of even large abscesses was noted, but the majority either ruptured or required incision and drainage to relieve the tension pain. Healing then took place, or a discharging fistula persisted, the opening of which sometimes became surrounded by the char-

acteristic papillomatous ulceration. The pus usually was thick and tenacious, making aspiration difficult, and varied in color from a light yellow to a dark red or brown, according to the amount of blood present.

Blastomycetes can usually be demonstrated in the pus by mounting it direct or mixing with a 20 per cent. solution of sodium hydroxid (Fig 1). In a few instances they could not be demonstrated either in smears, tissue sections or by cultures. Perhaps the most reliable method in such cases is the staining of a thin smear on a slide with hematoxylin and eosin, or with polychrome-methylene-blue. The degenerated forms can then be more easily recognized.

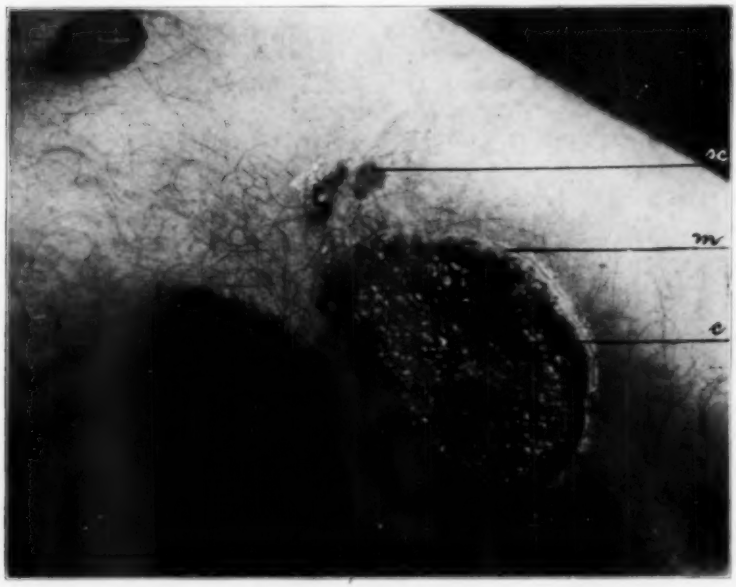

Fig. 22.—A typical lesion of cutaneous blastomycosis: (*e*) papillomatous or verrucose surface; (*m*) raised indurated border containing miliary abscesses; (*sc*) scar of old lesion. (By courtesy of Dr. O. S. Ormsby.)

The affections of the bone consisted of osteomyelitis, periostitis and arthritis. The osteomyelitis which is suppurative in its nature may be diffuse[13] or localized. In either case the fungi are very numerous, invading the narrow compartments and causing necrosis of the marrow cells, with the formation of a purulent exudate.[14] The bone partitions then disappear, the areas become confluent and an abscess is thus pro-

13. Figure 2, Case 19, article by Krost, Moes and Stober, this issue.
14. Figure 4, article by Krost, Moes and Stober, this issue.

duced. The process may involve the bone to such an extent that spontaneous fracture happens. Ruptures of these abscesses often occurred, causing extension to adjacent tissues. Such lesions in the ribs,[13] clavicle, sternum,[15] the bones of the skull, and the small bones of the hands and feet were important features in a number of cases. Formation of sequestra was observed in two instances.

In the long bones the infection has a tendency to lodge in the epiphyses,[16] and in some instances the shape of the infected areas strongly resembled those produced by infarcts.[17] Extension by rupture of the epiphyseal abscesses was responsible for the majority of the joint lesions.[18]

In those necropsies in which opportunity was afforded to study the changes in and about the joints, communication with abscesses in the adjacent bone were always found. In the cases in which suppuration of the joint was marked, more or less destruction of the synovial membranes, the articular ligaments and periarticular tissues was produced, often to the extent that subluxation occurred. The articular cartilages were sometimes so completely destroyed that the rough eroded bone was exposed.[19] Diffuse blastomycotic osteomyelitis of such an exposed head of the tibia was found in Case 21.[20] A healing periostitis was also present in this case. Special mention should be made of the spinal lesions because of the close resemblance of the symptoms produced to those of tuberculosis or Pott's disease. Spondylitis was present in Cases 7, 8, 18, 19, 23 and 28. The bodies of the vertebrae were affected in all except Case 23, in which the disorganization seemed to have occurred in the laminae and the posterior ligaments. More or less complete paralysis occurred in two cases.

A careful study of the appearances of the bone lesions in numerous roentgenograms was made by Dr. H. E. Potter, roentgenographer to the Cook County Hospital, and the following are his observations:

> In general the presence of blastomycotic infection of bone is easy of demonstration on account of the intense localized nature of the destructive process. In the first stages of the invasion no changes are visible; but as soon as destruction and absorption have advanced to a moderate degree the lesions are easily demonstrable. On the whole it has been our experience that the radiographic findings are more marked than in other types of infection presenting a similar clinical picture. Moderate pain, tenderness and swelling around a joint may be accompanied by a marked degree of bone involvement.

15. Figure 1, article by Krost, Moes and Stober, this issue.
16. Figures 4 and 5, article by Lewison and Jackson, this issue.
17. Figure 4, article by Myers and Stober, this issue.
18. Figure 3, article by Myers and Stober, this issue.
19. Figure 2, article by Lewison and Jackson, this issue.
20. Figure 4, article by Lewison and Jackson, this issue.

I have been fortunate in being able to obtain numerous skiagraphs at various stages of the disease from cases which were being studied exhaustively from a clinical and pathologic standpoint. The lesions which were skiagraphed and studied occurred in the spine, ileum, ribs, femur, tibia, fibula, scapula, humerus, radius, ulna, and in the wrists, hands, ankles and the feet. The following conclusions have been drawn from a serial study of the plates alone.

Skiagraphs of blastomycotic bone lesions show rarefactions and osseous proliferations not dissimilar in some respects to those seen in other types of bone infection. A comparative study of more than a score of these lesions in their different stages and degrees of activity has shown, however, that certain appearances are quite constant in blastomycosis and but seldom seen in other affections.

The lesions are most numerous and distinct in the long bones. Here they are first seen in the spongy portion near the epiphysis (Fig. 23) or, if the extremity bears no epiphysis, they lie in close relation to the articular surface (Fig. 24). A focus may remain single or others may appear in the vicinity, coalescing as they increase in size. Coincident with rarefaction a bony periostitis develops over the extremity of the diaphysis and may completely envelope it.

Fig. 23.—Lower end of radius and ulna. *R*, an early focus in ulna beneath epiphysis (*E*). R', R'' and R''' are early foci in radius. *P*, periosteal ossification.

The newly formed bone may in turn undergo a progressive dissolution as the inner necrosis advances, although an instance has been observed (Case 24) in which an arrested rarefaction was followed by a complete and persisting encapsulation.

The epiphysis remains quite uniformly intact unless the joint cavity has been involved; erosions are then seen on the articular face. The compact bone of the shaft has shown erosions on its surface secondary to a deep abscess in the overlying soft tissues. Such a bone destruction in the shaft may give the appearance of a primary focus within the bone, until a projection at another angle proves it to be superficial. I have not seen a case in which the attack on the compact bone from without has led to a penetration with the formation a medullary abscess.

In an involvement of the short bones, which indeed is quite common, the picture is that of multiple foci, general osteoporosis, and early invasion of adjacent joints, with a minimum of bony proliferation.

The usual appearance of well-marked necrosis and opposition seen in the ordinary lesions of the long bones is modified in those cases in which the clinical

course has been acute and in those which show a tendency to subside or heal. The former show gross destruction and limited proliferation, while the latter show a much greater proportion of newly formed bone. In an extremely rapid process the destruction may be complete, while the only evidence of opposition is seen on the shaft above the site of necrosis.

The bone surrounding the ordinary blastomycetic focus presents a normal structure with little tendency to change in density. This gives a rather sharp line of demarcation between bone apparently intact and regions of total necrosis. Such a marked localizing destruction occurring within the spongy bone of a diaphysis together with a mature and homogeneous periosteal proliferation with or without cloaca, is so constantly present in the ordinary lesions of blastomycosis that when seen in further skiagraphs where the etiology has not been determined, a careful search for blastomyces should be made.

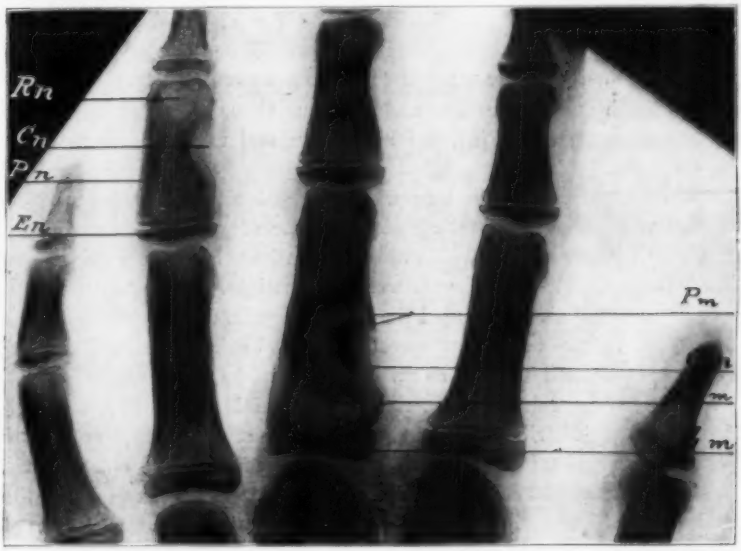

Fig. 24.—Phalangeal involvement; *m* shows coalescing foci beneath epiphysis (*Em, En*); *cm* shows a secondary breaking-down of proliferated bone (*Pm, pn*); *Rn*, a rarefication at a non-epiphyseal end of second phalanx. The same general characteristics are shown. A softening of the proliferated tissues at *Cn* is distinct. The adjacent joint is normal.

The pathological changes found in the respiratory system of eight patients in this series conform in a general way to those described in the eight previous reports of post-mortem examinations. Acute laryngitis and bronchitis were usually associated with active pulmonary lesions, and the pleurae also presented changes in accord with those found in the lungs. In cases with active pulmonary lesions, a serofibrinous pleuritis was quite a common finding and in one of our cases (Case 20) blastomycetes were isolated from the exudate. In other cases

fibrous pleuritis was present, often obliterating the cavities. The thickening of the pleurae at times was remarkable,[21] and the scars at the apices usually involved the adjacent tissues for some distance, in one case causing constriction of the jugular vein. Pus in the pleurae occurred but once, this in a localized empyema found in Case 19. Fistulous passages in the pleurae extending to a lesion of the spinal column were found in one of our cases (Case 23) similar to that observed in Case 7, and communication with the left bronchus was noted in Case 22.

A comparison of the lesions found in the lungs in these post-mortem examinations with those of eight previous reports, as mentioned before, suggests two methods of infection. In a few cases the bronchogenic type predominated, but the majority showed diffuse hematogenous infection, the primary foci existing as fibrous areas about the larger bronchi.

In the bronchogenic type much fibrous tissue existed, either solid or enclosing regions of infected lung tissue and usually located in the upper lobes.

In one case an upper lobe was converted into a fibrous mass in which were areas of necrotic material, some of which were associated with cavity formation and dilatation of the bronchi.[22] In marked contrast to such extensive fibrosis was the small area found in the lung of Case 21.[23] This represented the only change in the lungs of a patient who a few months before had presented clinical evidences of wide-spread pulmonary infection. The recent lesions consisted of small foci which have already been described as characteristic of blastomycosis; although in some cases distributed throughout the lobe or lung, they were quite discrete, and histologically such areas were often found unassociated with inflammatory changes in adjacent alveoli.[24] This may explain the indefinite physical signs which were obtained in the examination of lungs which at necropsy were found to be extensively involved. In other cases such foci had become confluent, forming larger areas of consolidation which were usually light gray.[25] Softening in the center of such areas was occasionally present. These focal lesions in some cases were distributed in such a manner as to suggest a bronchogenic origin.[26] In other cases, however, the wide-spread and uniform distribution closely resembled a miliary tuberculosis and could hardly have occurred except as a result of infection through the blood-stream. In the more severe

21. Figure 7, article by Krost, Moes and Stober, this issue.
22. Figure 1, article by Myers and Stober, this issue.
23. Figure 3, article by Lewison and Jackson, this issue.
24. Figure 3, article by Churchill and Stober, this issue.
25. Figure 3, article by Krost, Moes and Stober, this issue.
26. Figure 1, article by Boughton and Clark, this issue.

cases the infection was so marked that complete consolidation of the lung was produced, although here and there small nodules could be seen.[27]

Concerning lesions in other viscera our observations also correspond to those in previous reports in that focal infections were quite common in the spleen, liver and kidney.[28] Foci in the myocardium (Case 6), adrenal (Case 6), and pancreas (Case 5) had been found but once, and to this we are able to add instances of infection in the pericardium (Case 20) the adrenal (Case 26) and pancreas as well as four cases of blastomycotic abscesses of the prostate[29] (Cases 19, 20, 26 and 29), two of which were undoubtedly the source of the organisms found in the urine. Nephritis was more or less marked in all cases, myocarditis in a few, and acute endocarditis in one case (Case 21).

While lesions elsewhere have been quite numerous it is worthy of note that involvement of the brain has previously been noted but once. In the report of Case 7 a large abscess in the cerebellum together with lesions of the spinal dura and cord are described, and subsequently small lesions in the cerebrum were also discovered. In the four cases of this series (Cases 19, 21, 22 and 26) in which complete examination of the brain could be made, local lesions were also found. They consisted of small abscesses of variable size and location. In cases 19, 22 and 26 they were found in both cerebrum[30] and cerebellum,[31] and in Case 21, one solitary nodule was found in the pons. These have been discussed by Dr. LeCount.[32] The external cerebral dura was affected by extension of a bone abscess in Case 20, and the patient in Case 2 died of a meningitis, the blastomycotic nature of which was not determined. Such a process, however, had been anticipated and was found in the necropsy in Case 27 by Dr. LeCount. The spinal cord also was involved in Cases 18 and 23.

Of considerable interest is the existence of lymphadenitis in blastomycosis inasmuch as the slight tendency of the blastomycetes to invade the lymph-nodes has been dwelt on as a differential point between this infection and coccidioidal disease. A general enlargement of the lymph-nodes was found at necropsy in about one-third of the cases, and blastomycotic lesions in addition to having been found in the peribronchial lymph-nodes a number of times were on two occasions in this series also found in the submaxillary, axillary and inguinal lymph-nodes.

27. Figure 1, article by Churchill and Stober, this issue.
28. Figures 2 and 5, article by Myers and Stober, this issue.
29. Figure 2, article by Churchill and Stober, this issue.
30. Figure 6, article by Myers and Stober, this issue.
31. Figure 7, article by Myers and Stober, this issue.
32. LeCount, E. R., Jour. Nerv. and Ment. Dis., 1909, xxxvi, 144.

As a final supplement to the list and perhaps worthy of mention is the general infection of the eye which occurred in Case 20. Blastomycetes were obtained in pure culture from the vitreous humor, but no opportunity was afforded to study the pathological changes.

In a majority of the cases in which a careful history could be obtained, the patients stated that their illness began with a cold or an acute infection of the respiratory tract, more or less intense in degree. The more intense infections were sometimes preceded by a chill, and the symptoms most often noted were pain in the chest, fever, dyspnea, cough and expectoration of bloody and purulent mucus, to be followed sooner or later by the occurrence of the characteristic subcutaneous abscesses. In other cases the onset was less abrupt and the initial symptoms slight and transient, the first manifestations to attract the patient's attention being the appearance of the local ulcerations or abscesses.

After the disease became established the general symptoms were those of a chronic infection: malaise, loss of strength, emaciation, pain in the affected parts, irregular fever, rapid pulse and occasional chills and sweats. Emaciation and loss of strength were usually proportionate. In our cases the emaciation was extreme. The face became drawn and haggard and assumed an expression which impressed the observers as being somewhat characteristic. The enlargement of the affected joints presented a marked contrast to the emaciated extremities.[33]

The temperature was most irregular, sometimes high, and at other times normal or subnormal. In general, however, a fairly regular evening rise of temperature was present, and was usually associated with profuse perspiration. In one case the high temperature occurred in the morning. The pulse was usually increased in rapidity and often out of proportion to the temperature.

Symptoms of pulmonary infection occurred sooner or later in all, and in some constituted the principal manifestation, although in no cases were the symptoms or physical findings commensurate to the extensive lesions found in the lungs at necropsy. Cough was usually present, sometimes severe. The sputum was thick and purulent or mucopurulent in character, often containing blood. The latter was present in nearly all cases, but was irregular in occurrence and small in quantity. No marked hemorrhages occurred. Blastomycetes were present in the sputum in eight of the cases of this series, and in the mucus removed from the trachea at necropsy in the other two. They were also noted in the sputum in four of the other reported cases.

33. Figure 1, article by Wewison and Jackson, this issue.

Their demonstration is quite easy when examined in 20 per cent. solution of potassium hydroxid with a ⅛ inch objective (Fig. 25).

Respirations were increased, and in a few cases dyspnea and hoarseness were present. Sharp pains in the chest, due probably to the acute pleuritis, were not infrequent, but they rarely lasted more than a few days. The majority of the patients complained of a dull aching sensation in the chest. Of the physical signs, diminished expansion of the chest, due to fibrous pleuritis, was often found. Dulness on percussion, the presence of râles, and increased transmission of breath and voice sounds were frequently noted, but as already stated, were not present in a degree proportionate to the changes found in the lungs at the post-mortem examination. Areas of consolidation occurred first

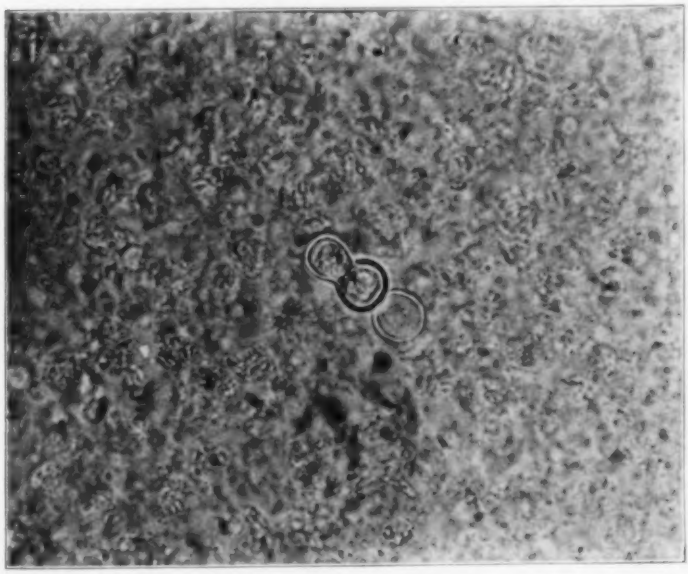

Fig. 25.—Round and budding forms of blastomycetes in sputum. Specimen mounted in 20 per cent. solution of sodium hydroxid. (Negative by Dr. W. A. Pusey.)

as a rule in the apices or upper lobes of the lungs, the right side being affected about three times as often as the left. Râles over the bases with no definite signs of consolidation were not infrequent. Very little gastro-intestinal disturbance was noted. Anorexia was a common feature, and diarrhea was present in five patients. Blastomycetes were found twice in the feces. The spleen was not constantly enlarged. Nephritis was not uncommon, and in several cases a marked edema occurred.

Albumin and casts occurred in the urine, and blastomycetes, having origin in abscesses of the prostate, were found in the urinary sediment in two cases of this series.

Pain was a constant factor in connection with the abscess formations, especially those involving the bones. This was caused by the pressure of the enclosed pus, and relieved by incision and drainage. The pain and tenderness in the affected joints at the onset were not so marked as in articular rheumatism, and not nearly so severe as would be expected with such extensive destruction as usually occurs later in the disease. Insomnia because of the pain was a prominent feature, and without doubt caused the marked irritability and melancholia of some patients.

Lesions of the spinal cord were responsible for paralysis of the lower extremities, and the involuntary discharge of urine and feces in two cases. No symptoms were produced by the lesions in the cerebrum, but this could hardly be expected from their size or location. One patient (Case 7) in whom a larger cerebellar abscess was found died during a convulsion, and signs of meningitis were manifested in one instance (Case 27). Marked neuralgic pain and gradual loss of vision, due to blastomycosis of the eye, were among the first symptoms noted in Case 20. The infection was located in the posterior chamber, and caused adhesions of the iris, irregularity of the pupil, opacity of the cornea, and marked congestion of the conjunctiva with purulent discharges.

The blood showed a reduction in the number of red blood-corpuscles and the hemoglobin percentage that would be expected in a secondary anemia of such a chronic infection. A leukocytosis is usually present, in some cases running as high as 30,000 per cubic millimeter. The average number of leukocytes in the reported counts, excepting a few in which the influence of sepsis distorted the blood-picture, was 16,800 per cubic millimeter. The average differential count was as follows: polymorphonuclears, 73 per cent.; small mononuclears, 17 per cent.; large mononuclears, 6.3 per cent.; transitionals, 0.7 per cent.; eosinophils, 1.5 per cent.; basophils, 0.1 per cent.; myelocytes, 1.4 per cent. In one case the myelocytes constituted 8 per cent. The mononuclear elements are relatively increased. This was more pronounced in those cases in which leukocytosis was less marked, as for example, one of the lowest counts (9,500 per cubic millimeter) showed only 55 per cent. polymorphonuclears.

The essential factor in the diagnosis of this disease is the demonstration of the blastomycetes in the sputum or in the pus of various lesions. This can usually be done so easily that there would seem to be no excuse for not recognizing the disease when it exists.

It should be remembered, however, that the organisms are easily overlooked in stained preparations, and the examination of fresh material is not a common routine measure. It happens, therefore, that the organisms in most cases have been found only when sought for, and when the nature of the disease has been suggested by its clinical or pathological features.

Blastomycosis should be ruled out in all cases of chronic pustular or ulcerative lesions of the skin, wasting pulmonary diseases, spontaneous superficial or deep abscesses, especially when connected with the bones, suppurative arthritis and suspected Pott's disease.

DIFFERENTIAL DIAGNOSIS

The conditions with which blastomycosis has most often been confounded and the important differential points will be briefly enumerated.

Coccidioidal Granuloma.—This disease has been ably discussed in the articles by L. Hektoen[1] and O. S. Ormsby.[2] That the disease from a clinical and pathological point of view closely resembles blastomycosis is generally conceded. The principal differential points advanced by the various authors are that in coccidioidal granuloma the nodular lesions resemble more closely those of tuberculosis, there is a greater tendency to involvement of the lymph-nodes, the cutaneous lesions are more ulcerative, the average duration of the disease is shorter than in blastomycosis, and reproduction of the organism in the tissues occurs principally by endosporulation.

Epithelioma.—The cutaneous lesions in Case 19 and also in other cases were first regarded as epithelioma, but close observation should readily differentiate these conditions. The principal points are the slower growth of epithelioma, the greater induration—extending into the tissues beyond the ulcer margin, and the absence of the bluish-red halo surrounding the border, which contains the characteristic miliary abscesses, and in which the blastomycotic organisms are usually found.

Tuberculosis.—Reference has already been made to the close resemblance between blastomycosis and tuberculosis, both clinically and pathologically. So far as the symptoms of the pulmonary infection are concerned, the clinical pictures of the two diseases are so similar that differential diagnosis is extremely difficult. Tuberculosis is the more destructive of the two, and cavity formation and marked hemoptysis are therefore more common. The examination of the sputum in most cases, of course, gives positive evidence of the condition present, and blastomycetes should be looked for in those cases of suspected tuberculosis in which the tubercle bacilli are persistently absent.

The affections of the bones are also very similar. The small bones and joints are perhaps more often affected in blastomycosis, the lesions

are more often multiple, and associated pulmonary, cutaneous and subcutaneous lesions are more common. It should be noted that in several cases the blastomycotic ulcerations of the skin were mistaken for lupus. A very interesting and important point emphasized in Case 23 was the marked simulation of Pott's disease by the blastomycotic lesion of the spine. If any differences exist it might be stated that blastomycosis is more painful and rapid, and may begin by extension from the pleurae or adjacent structures rather than in the bodies of the vertebrae.

The tuberculin reaction was tried in several of the cases in this series, with negative results.

Syphilis.—Some of the pustules and ulcerations might be mistaken for syphilitic lesions and the hard indurated character, with subsequent softening of the deep abscesses, is suggestive of gummata. Roentgenograms of the affected bones have shown osteoporosis and periosteal thickening almost identical to that produced in syphilis, and one might be further mistaken and misled by the improvement which follows the administration of potassium iodid.

Inasmuch as positive diagnosis of obscure cases of syphilis are now being made with the Wassermann serum test, and it being realized that this is a group reaction, it was deemed of interest to try the reaction with blastomycosis. The serum in two cases was tested by Dr. F. G. Harris. One proved negative and the other was positive. It was assumed that the latter patient was at one time affected with syphilis, although no history could be obtained. The blastomycetic vaccine reaction may prove to be a positive factor in the diagnosis of blastomycosis. In three cases of blastomycosis in which cutaneous lesions were present, a distinct inflammatory reaction was observed in the local lesions after the injection of the blastomycetic vaccine filtrate. In the two cases which were not so far advanced a rise of temperature was obtained in from six to twenty-four hours after injection, the temperature in some instances persisting for two or three days. Such a rise in temperature did not occur in two cases of syphilis, three cases of tuberculosis and three normal persons who were subjected to the test.

Cutaneous tests consisting of the application of the filtrate and also triturated cultures in lanolin to scarified areas provoked no reaction sufficiently distinct to be considered specific. Ophthalmic tests with the filtrate were also negative. Different results might have been obtained with the use of cultures killed with less heat or in some other manner inasmuch as the ones used were subjected to a temperature of 110 C. (230 F.).

Dr. Boughton, using suspensions prepared by Dr. L. Hektoen, noted the formation of small nodules at the site of puncture and inoculation

after the method of von Pirquet. These did not occur in a subsequent test. Other cutaneous and ophthalmic tests with these suspensions were negative.

PROGNOSIS

Experience to date indicates that the prognosis is extremely grave, the mortality thus far constituting nearly 90 per cent. It should be remembered, however, that in the majority of the cases the diagnosis was not established until the patients were in an extreme condition, and in several instances at necropsy. The recovery in three cases (Cases 2, 13 and 24), the remarkable temporary improvement and the evidence of healed lesions in the lungs at necropsy in Case 21, and the healed and healing lesions of the lungs, pleura, peribronchial lymph-nodes and bones in Case 23 of this series, would indicate that the infection can be overcome by the system, and that with early diagnosis and proper treatment the mortality can be much reduced. An important point to be remembered in connection with the prognosis given regarding local lesions is that live blastomycetes may persist for some time in the tissues of apparently healed regions of infection and again become active when treatment is discontinued or the patient's vitality reduced.

The duration of the illness has varied from four months to two and a half years. More than half the patients were sick for a period longer than one year. In many of the cases death was due to secondary pyogenic infection.

TREATMENT

Prophylaxis.—If the previously mentioned theory of infection should prove to be true, prophylaxis could be rather easily established. Pulmonary infection arising from the inhalation of mold spores could be prevented by the proper ventilation, lighting and drainage of residences and shops, thus preventing the dampness and moisture, which favor mold growth. Cutaneous infection could also be avoided by the careful cleansing of wounds received in the presence of decaying or moldy wood or other vegetable material.

Medical.—The influence of food, climate and hygienic measures is undoubtedly as beneficial here as in any other chronic infection. The recovery and cure in Case 13 was ascribed to climatic influence. Of specific medication, potassium iodid in large doses seems to have the greatest effect. It has been used successfully in a number of cutaneous infections, and was given credit for the cure in Case 2. It was also administered for a time in Cases 13 and 24, mentioned before as cured, and in Cases 21 and 23, in which an improvement at least of the pulmonary condition was manifested. (The internal administration of copper sulphate seemed to be of no benefit.) For the cough,

pain and insomnia, codein is especially valuable, although in a few instances morphin was necessary. While medical treatment proved of benefit for the pulmonary infection, its influence on the metastatic lesions was not so marked, and these appear to be the cause of death in a number of instances. In the histological examination of the bone and subcutaneous abscesses, one is impressed with the fact that the extension and increase in size of the infected areas is often directly due to the pressure of the growing fungi, and surgical interference would therefore be indicated to a greater extent than has been employed. Clinically, excision of the cutaneous lesion has been very successful, and the relief of tension pain was always obtained by aspiration or drainage of the abscesses. In a few cases healing of abscesses was affected by this alone. Curettement of the bone abscess in Case 23 resulted in prompt healing, although reinfection occurred several months later.

Solutions of copper sulphate and iodin were applied to the ulcers, but with indifferent results, probably for the reason that the solutions do not penetrate to a sufficient depth to reach the organisms. Much better results were noted when these solutions were employed for irrigation of the abscesses. The Roentgen rays have proved very beneficial in the treatment of the cutaneous lesions, but they were not used to any extent in the cases of this series.

VACCINE THERAPY

Vaccination with blastomycetes and their products for therapeutic purposes was performed in three cases, two systemic cases (Cases 24 and 26) of this series, and one case of cutaneous infection (Fig. 40). The latter was in the service of Dr. O. S. Ormsby, through whose courtesy the treatment was instituted.

The material used consisted of the filtrate and the suspension of the triturated membranes of bouillon cultures grown at room temperature for periods varying from two to six months. The cultures were killed by heat (110 C.) and preserved with 0.8 per cent. chloretone. Subcutaneous injection of either the filtrate or suspension produced an area of induration varying in size according to the quantity used. A few of the larger areas became soft and fluctuating, owing to the formation of pus, which was sterile in all instances examined. Such indurations and abscesses were more constant and pronounced when the suspension was used, and did not occur with small quantities of the filtrate. A certain amount of pain was noted the first few days at the site of injection.

The general effect of such injections was usually a rise in temperature of from one-half to two degrees.[38] This became apparent in

38. Figure 4, article by Boughton and Stober, this issue.

from six to twenty-four hours and sometimes persisted seventy-two hours or longer. With the rise of temperature occurred a feeling of general malaise and pain in the back and extremities. Pain, however, was more especially manifest in and about the local lesions, in which a distinct inflammatory reaction occurred, consisting of pain, swelling, increased discharge, and often bleeding from the ulcerated surface. This receded in from twelve to forty-eight hours. The crusts became detached, the ulcers decreased in size and general improvement followed. Deep abscesses approached the surface and ruptured, and healing of old fistulas occurred. These effects were quite as apparent from small amounts of the filtrates as from larger amounts of the emulsions. The latter produced more general disturbance and temperature; in fact, a rise of temperature was noticed in three cases not blastomycotic in which sterile abscesses followed the injection of 4 c.c. of the emulsion.

The reactions mentioned above occurred most typically in Case 24, in which improvement began with the first injection, and was continuous. After four months the patient felt well and strong, and of twenty-four lesions which were present at the beginning of the treatment, only two remained and these were in an advanced stage of healing. Two months later, however, one of these again became active and a new cutaneous ulcer appeared. Vaccinations were again resumed with the result that the lesions again are practically healed.

In Case 26, however, such good results were not obtained. The patient was in such poor condition when treatment was instituted that a different outcome could hardly have been expected. On July 10 an injection of 1.2 c.c. vaccine filtrate was followed by pain in the chest and a severe cough, lasting for two days. No increase of temperature or local reaction occurred. Six days later an injection of 1 c.c. of the filtrate produced a rise in temperature of 1.8 F., but no pain occurred in the local lesions or in the chest. On July 22 an injection of the same amount provoked only a slight rise in temperature, but a decided reaction in the superficial lesions was noted. Slight burning and itching were felt by the patient during the night, and the next day the margins of the ulcers became soft and the crusts dropped off. Apparent healing occurred for a few days, when the general condition of the patient became much worse. Cultures from pus aspirated from the various abscesses at this time showed no blastomycetic growths, but many staphylococci and a few streptococci were present. There were, however, a few blastomycetes found in the sputum, and it is interesting to note that nearly all were contained in giant-cells, a condition which was not previously observed.

On August 8, 2 c.c. of the filtrate were given, with very little success, and 3.5 c.c. on August 21 produced no reaction whatever. Dur-

Fig. 26.—Case of cutaneous blastomycosis in which vaccines were used. (Courtesy of O. S. Ormsby.)

ing this time the patient had been gradually failing, and death occurred six days later.

The case of cutaneous blastomycosis (Fig. 26) was under treatment for two months, and at first some startling results were obtained. These, however, were only temporary. The patient was very anemic when he entered the hospital, the hemoglobin, estimated by the Dare instrument, amounting to 28 per cent. This was reduced by the repeated hemorrhages until only 12 per cent. was present. At this time the patient was unconscious and very weak. An arm-to-arm transfusion from a convalescing blastomycotic patient by Dr. Schroeder was followed by a rise to 27 per cent. and such an improvement in the patient's condition that consciousness returned, the dyspnea disappeared and he was able to sit up and partake of his food the following day. After a weak, however, he again became worse and died two days later.

From a most conservative point of view, the limited experience with this method of treatment is very encouraging and suggests that the injection of the filtrate of old blastomycetic cultures may not only be useful in diagnosis, but also prove to be a valuable therapeutic measure.

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†Since this article was completed a summary of the literature, together with a case report by Dr. Harter, has been brought to our attention. The bibliography of the work is most complete, especially the references to foreign literature.

A CASE OF SYSTEMIC BLASTOMYCOSIS*

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CASE XIX (1).[1]—*History.*—M. L., aged 42, married, a native of Poland and laborer by occupation, had lived in the United States four years. He was admitted to the Cook County Hospital April 8, 1907, to the service of Dr. Loeb with the diagnosis of acute articular rheumatism, because of the obvious swelling of the hand and foot.

After admittance to the ward, the following history was obtained with the aid of an interpreter: About four months before admission he was taken with a severe cold, cough and expectoration. This interfered but little with his general health. He next noticed a pain in the back, at first felt only on motion, later when lying on the back. A month later a swelling appeared at this painful area in the thoracic region, at the left of the median line. The cough, which persisted from the onset, became more marked, with abundant expectoration. His appetite began to fail and he noticed that he was losing weight. About four weeks before admission blood was present in the sputum for several days; the general weakness became so pronounced that he was compelled to stop work six weeks after the onset. Two months before admission painful swellings developed successively on the back of the left hand and foot and in the chest wall on the left side over the eleventh rib. The next lesion appeared three weeks before admission as a small papule on the right ala of the nose. This was quite painful and developed slowly into a warty growth. A week later enlargement of the submaxillary lymph-nodes on both sides of the neck was noticed. He complained of cough, profuse expectoration, night sweats, marked general weakness, and pain in the affected parts. He denied previous illness of either a general or specific nature. The family history was unimportant, except that his first wife died of tuberculosis. Three children born by his second wife are healthy. The patient had been a coal-heaver the past four years, and his habits were good.

Examination.—The patient was a middle-aged man, considerably emaciated, and very anemic. He lay on the right side and suffered with much pain on even slight movements involving the affected parts. The skin was moist, and perspiration especially profuse on the forehead and in the axillae. The respiration was free and rapid, averaging thirty per minute. The pulse was full and regular, the temperature 99.8 F., the scalp normal, the face drawn, the cheeks sunken, and the eyes partly closed. The pupils were dilated, equal and reacted to light and accommodation. There was no nystagmus or evidence of ocular paralysis. In the middle of the forehead was a small papillomatous growth covered with a thin yellow crust. On removal of this crust a small quantity of pus appeared. The margin was indurated red and sharply demarcated from the surrounding skin. At the margin of the right ala of the nose was another larger growth, 1.5 cm. in length. The papillomatous character was more distinct; it extended

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* Reported in part in Jour. Am. Med. Assn., 1908, l, 184.

1. Roman numerals in this and the following articles refer to number given in bibliography according to publication or occurrence. Arabic numerals refer to number in this series.

into the nostril for a distance of 0.5 cm., and was associated with considerable swelling of the adjacent tissues. The left ala of the nose was red, swollen and indurated, but the overlying skin was smooth. All these areas were very tender. The nasal cavity, mouth and pharynx were much congested with marked formation of mucus. No growths were visible, and the tonsils were not enlarged. The tongue was dry, the dorsum covered with a brown coat, the margins bright red. The teeth were in poor condition, many showing marked decay. In the submaxillary region on both sides of the neck was a hard, round, deep-seated swelling about the size of a walnut. The anterior and posterior cervical lymph-nodes presented a slight enlargement. No cervical rigidity was present. The thyroid was small and irregular. The bony framework of the chest was prominent, owing to the marked emaciation. Over the sixth rib on the left side in the nipple line was a rounded swelling about 2 inches in diameter. The overlying skin was red and adherent to the mass, and slight fluctuation was present. Posteriorly, on the right side over the twelfth rib, was another swelling of the same size, but the skin was not adherent and it did not fluctuate. Directly over the spine extending from the level of the eighth thoracic to the first lumbar vertebrae, and measuring 3 inches transversely, was still another swelling fluctuating and adherent to the overlying skin. Pressure over these areas excited marked pain.

Expansion of the chest was slightly retarded on the right side. On percussion the lungs showed no changes anteriorly. Posteriorly, dulness was obtained over the lower lobe of the left side, and over a small area below the angle of the scapula on the right side. On auscultation of the lungs anteriorly a few bubbling râles were heard. On the left side over the upper part of the area of dulness the same signs were present, and whispered and voice sounds increased in intensity. At the base these râles were audible, but the breath sounds were suppressed.

The heart was slightly enlarged to the left. The apex beat was palpable in the fifth interspace in the nipple line. A slight murmur could be heard over the apex, but it was not transmitted to the left; other sounds were normal.

The abdomen was scaphoid. On percussion and palpation no abnormalities were noted. The liver and spleen were not palpable. The genitalia were normal. The lymph-nodes of the inguinal region were enlarged, forming a continuous chain on each side. On the dorsal surface of the right forearm were two small papillomatous growths, which resembled closely the one on the forehead. Considerable pain was elicited by deep pressure on the muscles of the forearm, but no swellings could be detected.

The left hand and foot were diffusely swollen, especially on the dorsal surfaces. The middle finger also showed a diffuse enlargement, being nearly twice as large as normal. These swellings were characterized by pain, fluctuation, tenderness and slight redness of the overlying skin. Examination of the nervous system revealed nothing abnormal.

Diagnosis, Treatment and Course.—The patient's condition aroused considerable interest and was diagnosed syphilis, pyemia and tuberculosis by different observers, the growth on the nose being generally regarded as epithelioma. Inasmuch as the diagnosis of syphilis was regarded as the most probable, the patient was given potassium iodid, 20 grains, and the protiodid of mercury, 1/5 grain, four times daily, with the effect of marked softening of the swellings. The potassium iodid was continued for a number of weeks, after which quinin and acetylsalicylic acid were administered.

On April 19 the character of the nasal growth was recognized and a diagnosis of generalized blastomycosis was made. Blastomycetes were then demonstrated in smears of pus from the nasal growth. The organisms were also found in the sputum, urine sediment, and the aspirated contents of the swellings of the left hand and foot. The nasal growth was then excised and sectioned in celloidin. Microscopic examination showed changes typical of those described as occurring in blastomycosis of the skin. The epidermal layer presented a hyperplastic thickening with marked irregularity of the papillae. Scattered throughout were

numerous intra-epithelial abscesses densely packed with lymphocytes, desquamated epithelial cells and polymorphonuclear cells, the latter predominating. Blastomycetes were present as round or oval refractile bodies, singly or in clumps, and budding forms were present. No giant-cells were present in the purely intra-epithelial abscesses, but they were quite numerous in the cutis. Here the cellular infiltration was dense, and, except in a few areas, the mononuclear cells predominated. Many plasma-cells and eosinophils were present. In several places the blastomycetes were found in the giant-cells. Attempts to isolate the blastomycetes in pure culture resulted in failure, because of the numerous other organisms present.

Blood-cultures at this time yielded the organisms, 5 c.c. of blood from the median vein being distributed equally into ten large test-tubes, each containing 10 c.c. of ordinary bouillon. After incubation for three days, two discrete white colonies were observed in one of the tubes, suspended in the fibrin meshes which permeated the fluid. These grew rapidly and began to show a distinct radiating structure. From one of these a smaller colony gradually separated by its own weight and was later removed for examination and subculture, to which reference will be made later.[2] The removal of this colony, which showed a distinct blastomycotic structure, resulted in the dissemination of organisms in the bouillon, for in a few days about thirty secondary colonies were observed scattered through the medium. By this time the original colonies had attained a diameter of 5 mm., the margins showing a fluffy radiating structure, while the center was becoming clear and indistinct. Pure cultures were easily obtained from the abscesses.

April 24 the red blood-cells numbered 2,420,000 per cubic millimeter, the white cells 14,200. A differential count of 200 cells showed polymorphonuclear neutrophils 67 per cent.; large mononuclear leukocytes, 9 per cent.; small mononuclear leukocytes, 16 per cent.; eosinophils, 2 per cent.; myelocytes, 3 per cent., and transitional forms, 2 per cent. May 8, the white cells numbered 22,800 per cubic millimeter. Still another examination on May 16 gave a red-cell count of 2,280,000 per cubic millimeter. The hemoglobin was estimated at 70 per cent. (Tallqvist). The leukocytes numbered 29,800. A differential count showed 77 per cent. polymorphonuclear neutrophils; 7 per cent. large mononuclears; 6 per cent. small mononuclears; 1 per cent. eosinophils, and 8 per cent. myelocytes.

On April 4 the urine possessed the following features: color, amber; specific gravity, 1.015. No sugar or albumin present. Diazo reaction negative. The sediment contained a few leukocytes. No red blood-cells or casts were present. An examination on April 25 gave about the same results, except that the sediment contained a few hyalin casts and leukocytes, and a large number of round and oval refractile bodies possessing a double contour and staining poorly with methylene blue. On May 6 there was little change, except that the specific gravity was high, being 1.028. A careful study of the refractile bodies found in the sediment left no doubt as to their character, as they did not dissolve in a 40 per cent. solution of potassium hydroxid, and presented numerous budding forms. They undoubtedly came from the pus from the abscesses in the prostate which were found at necropsy.

The sputum, which was abundant, was of a yellowish purulent character, with varying amounts of blood, which at times were sufficient to give it a brick-red or chocolate color. It was thick, but not tenacious. Repeated examinations failed to demonstrate tubercle bacilli in it. Many blastomycetes were found in the potassium hydroxid preparations. Nothing of importance was found in several examinations of the feces.

The patient became gradually worse and was helpless and bedridden after May 18. He complained bitterly of pain in the affected parts, especially on

2. This is the second case in which the organisms have been recovered from the blood, the first instance having been recorded by Buschke.

motion, or when the abscess walls became tense from pressure of the enclosed pus. Evacuation of these gave marked relief.

The appetite continued fair, but in spite of this, he continued to lose flesh until the emaciation became pronounced. No nausea or vomiting occurred at any time. The bowels were fairly regular. Urination was normal. His sleep was often disturbed by the pain occasioned by involuntary movements about the bed. Perspiration was profuse and constant. His mental condition was very good, but became irritable and morose toward the end. The cough was not especially marked at any time, but the expectoration was profuse. The local lesions progressed more or less rapidly. The induration about the nasal lesion excised April 19 extended into the nostril for some distance, and it is probable that not all of the infected tissue was removed, as the wound again took on a papillomatous appearance. The opposite ala became red and swollen, and the surface covered with a thin brown crust. The abscesses on the hand and foot became soft and were aspirated April 19. Marked relief from pain resulted for a few days, but it became necessary to incise and drain a few days later. The pus obtained was thick, and varied in color from a light yellow to a dark brown. The abscesses on the back also were aspirated and the one on the left side of the chest incised May 15.

During this time new abscesses formed in the right forearm and hand and in the inner part of the left thigh. These were subsequently opened and pus of a similar nature evacuated. With one exception, the discharge from these abscesses had been continuous and profuse, and a distinct moldy growth occurred on some of the dressings in which the discharge had become dried.

There was a morning elevation of temperature, with marked evening remission, the latter often subnormal, at one time as low as 96 F. The high points ranged between 100 and 102 F. until the last two weeks, when temperatures between 102 and 103.8 were recorded. The pulse continued fairly steady between 100 and 120 per minute until two weeks before the patient's death, when it began to follow the temperature curve, going as high as 140. During the last four days of his illness it varied between 120 and 160, the temperature being subnormal. The respirations averaged about 26 per minute, and did not show any marked variations until the last week, when they also became more rapid. During the last four days they were rapid and labored, from 54 to 60 per minute until the end. Death occurred June 14 from exhaustion.

Necropsy.—Permission for a necropsy was secured three days after death and the following anatomic diagnosis made: miliary and nodular blastomycosis of the lungs, kidneys, spleen, cerebrum, pleura and lymph-nodes. Multiple blastomycotic abscesses of the cerebrum, cerebellum, prostrate, pleura, skin, osseous, muscular and subcutaneous tissues. Parenchymatous nephritis. Fatty changes, adenoma and angioma of the liver. Adenoma of the thyroid. General lymphatic hyperplasia. Shaven beard appearance of Peyer's patches. Atrophy of the testicles. Fibrous pleuritis.

The body was that of a middle-aged man 177 cm. (5 feet 10 inches) in length, and extremely emaciated. Considerable post-mortem lividity and some edema of the feet and ankles were present. The surface of the body was marked by a number of fistulas and elevated swellings, from 2 to 8 cm. (4/5 to 3 inches) in diameter and of three general types: a distinct papillomatous growth with a raised surface occasionally covered by a thin brown crust, the margins indurated and surrounded by an areola of discoloration. The second, excavated areas from 1 to 3 cm. (2/5 to 1 inch) deep, with granular friable bases exuding a thin serum. A third variety were lesions covered by thick brown rupia-like crusts removed with difficulty and resting on a bed of yellow pus. The bases of the ulcers thus formed were much more granular than those of the second variety. The last two varieties seemed to involve the subcutaneous tissues to a greater extent and suggested these as the point of origin. These lesions were distributed in the skin

over the right upper lip, right eyebrow, knee, elbow and costal margin, the left cheek and on both alae of the nose.

The fistulas were either open and discharging a thin yellow pus or were covered by a brown crust. They were located on the inner side of the left foot, dorsal surface of the right hand and radial sides of both forearms. All were the results of operation, none of the abscesses having ruptured spontaneously. The subcutaneous abscesses varied in size from 1 to 6 inches in diameter, and were soft in consistency and distinctly fluctuating. The overlying skin was pale usually, freely movable over the swelling, and an edema of the adjacent soft parts was noticeable. On incision a variable amount of thick pus escaped from a bright yellow to a reddish brown in color, according to the amount of blood present. The walls of the abscess cavities were smooth and thin. Some were confined to the subcutaneous tissue and others communicated with cavities in muscle or bone. Those confined more or less to the subcutaneous tissues were located as follows: on the left side over the eleventh and twelfth ribs, one measuring 5 cm. (2 inches) in diameter. It lay just underneath the skin, to which it was adherent. Another of about the same size was present at a point on the right of the spine opposite the fourth and fifth thoracic vertebrae. Below this, directly over the spine, from the sixth thoracic to the third lumbar vertebrae, and extending to either side a distance of 6 cm., was a large fluctuating abscess. It contained a large quantity of pus and extended deeply into the muscles, exposing the seventh and eleventh ribs, and the ninth, tenth, eleventh and twelfth thoracic and the first lumbar vertebrae, the spine of the ninth thoracic being almost completely eroded, the others showing only slight involvement. The muscles in the neighborhood had undergone pressure atrophy. About an inch below this and to the left of the median line was another large fluctuating abscess 9 cm. (3½ inches) in diameter.

The abscesses in the muscular tissues seemed to be located between the muscles, separating them from each other and adjacent structures. Some of these, by extension, were subcutaneous. The walls of all were thin and smooth with a noticeable absence of ragged necrotic tissue. After removal of the pus and cleaning some of the cavities it was almost impossible to locate the boundary. In the submaxillary region was an abscess lying beneath the platysma and sternomastoid muscles. It extended 6 cm. (2½ inches) traversely and 4 cm. (1½ inches) in a vertical direction. Posteriorly, the great vessels of the neck were exposed. Another 20 cm. (8 inches) in length and 6 cm. (2½ inches) transversely was contained between the muscles of the thigh. Its floor was formed by the muscles, semitendinosus and semimembranosus, separating the gracilis and the biceps. The wall was made up of recognizable surrounding structures, and it was covered by fascia and skin. No communication with the bone existed. In the right forearm on the radial side was a large swelling extending from the wrist to within 3 inches of the elbow, an abscess between the extensor communis digitorum and skin, and the extensor carpi radialis brevis. It had no distinct wall or communication with the bone.

The abscesses involving bones were either confined to them or communicated with collections of pus in the adjacent soft parts.

The sinuses on the dorsal surfaces of both hands led into small abscess cavities between the tendons and bones of the hands communicating with diffuse infiltration of the deep palmar tissues. In the left hand, one-half of the shaft of the third and fourth metacarpal bones alone remained. Slight erosion of the adjacent superior surface of the os magnum and the unciform was present. On the middle of the left foot was a large abscess communicating with a cavity in the body of the internal cuneiform. An incision into the right ankle revealed a diffuse infiltration of pus in the tissues about the joint with erosion of the internal malleolus. The right knee-joint contained turbid fluid, and the synovial membrane was finely granular.

Directly over the sternum was an abscess 2 inches in diameter which communicated through a small opening with an abscess in the bone. This cavity measured ¾ inch in diameter and extended to the periosteum on the posterior surface (Fig. 1).

The seventh rib on the right side about the middle of the shaft contained an abscess 2 cm. (¾ inch) in diameter, communicating through a small opening in the periosteum on the internal surface with another collection of pus between the layers of the pleura. This rib when split down the center to the costal end appeared normal to within an inch anterior to the abscess (Fig. 2). From this point to almost the costal end the marrow was yellow. The cancellous bone was softer than normal and the spaces were filled with a purulent material, which, on examination, showed many blastomycetes singly and in clumps.

The deep cervical lymph-nodes were enlarged and fused, forming continuous masses on either side, about 3 inches long, and an inch in diameter. The majority were firm and light yellow. On section small yellow nodular elevations 3 mm. (⅛ inch) in diameter were seen. Others were softer and contained calcareous masses. The inguinal lymph-nodes were also enlarged, the largest on the left side measuring 1 cm. (½ inch) in diameter. The submaxillary, superficial cervical and axillary lymph-nodes were also somewhat enlarged, but did not show the nodules or softening. Both pleural cavities were obliterated by fibrous adhesions, and the lungs were removed with difficulty.

The left lung weighed 1,340 gm. (about 3 pounds). The pleura was thin and was covered with numerous fibrous tags. A number of miliary nodules could be seen and felt beneath its surface. The lung was firm, did not collapse and crepitated feebly throughout. On section, the cut surface was grayish-black and diffusely infiltrated with small white or gray nodules from 1 to 4 mm. (1/25 to 3/16 inch) in diameter. The intervening pulmonary tissue seemed normal and on pressure exuded a clear, frothy fluid. Sections from the posterior portions where the nodules were confluent floated low in water. Except for a small area, 1 cm. (½ inch) in diameter, in the center of the lower lobe, no softening was present. Considerable purulent mucus could be expressed from the bronchi, and in this a number of blastomycetes, some of which were budding, were found.

The right pleural layers were united into a white fibrous coat most pronounced on the lower part of the lung, where it measured several millimeters in thickness. Between its layers over the lower lobe and communicating with an opening in the periosteum of the seventh rib was the collection of pus already mentioned, occupying an irregular space measuring approximately 6 by 4 cm. (2¼ by 1½ inch.)

The right lung weighed 1,900 gm. (4 pounds 3 ounces). It did not collapse and crepitated throughout. On section (Fig. 3) its appearance was very similar to that of the left lung, except that in the lower lobe the nodules were more confluent and formed irregular grayish-white solid regions 1 cm. (½ inch) or more in diameter. No softening was present. In the upper part of the lower lobe there was considerable fibrous tissue about the larger bronchi.

The larynx, trachea and bronchi contained a large amount of frothy, purulent mucus. The mucous membrane was smooth. The peribronchial lymph-nodes were enlarged and firm. On section they were black and contained a few yellow regions from 1 to 3 mm. (1/25 to ⅛ in.) in diameter. Others with no coal pigment were softer in consistency, translucent, and grayish-red on section.

The thyroid weighed 40 gm. (1½ ounce). The left lobe was much larger than the right. Little normal thyroid tissue was present, the entire gland being made up of numerous round encapsulated regions from 0.5 to 2 cm. (3/16 to ¾ inch) in diameter, on section from gray to light brown.

The pericardial cavity contained about 4 ounces of yellow fluid. Its layers were normal. The heart weighed 200 gm. (7 ounces) and presented no gross changes. The aorta had a few puckered areas of thickening in the arch. The

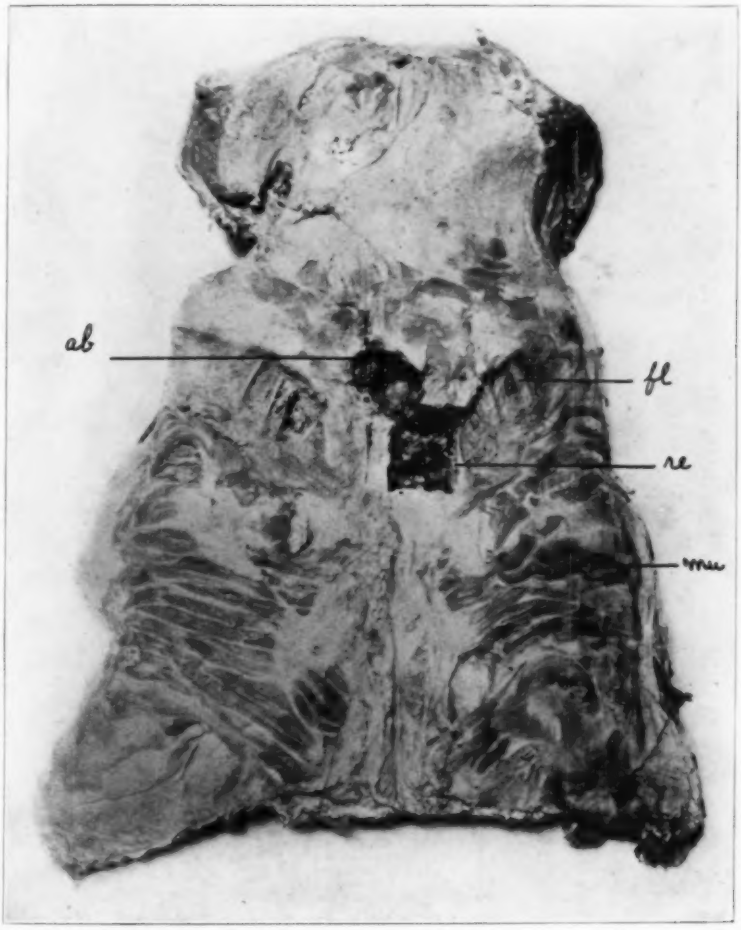

Fig. 1.—Blastomycotic abscess of the sternum: *mu*, pectoralis muscle; *ab*, the opening into an abscess in the gladiolus, the extension of which can be seen in that area where a rectangular portion (*re*) has been cut away. This lesion communicated with a large subcutaneous abscess the floor (*fl*) of which can be seen.

periaortic lymph-nodes were enlarged and grayish-red, and contained small yellow nodules.

The pharynx and esophagus were normal. The tonsils were small and had large crypts containing a small amount of mucopus. The peritoneal cavity contained a small amount of clear fluid. The peritoneum was smooth. Fibrous adhesions were present between the liver and colon, about the appendix and about the posterior margin of the spleen. The omentum was devoid of fat. A considerable degree of gastro-enteroptosis was present.

The stomach and pancreas showed only post-mortem changes, the intestines the shaven-beard appearance of Peyer's patches.

The gall-bladder and ducts were normal.

The liver weighed 1,900 gm. (4 pounds 3 ounces). The right lobe was enlarged and bore the imprint of the ribs. The surface was smooth, yellow and

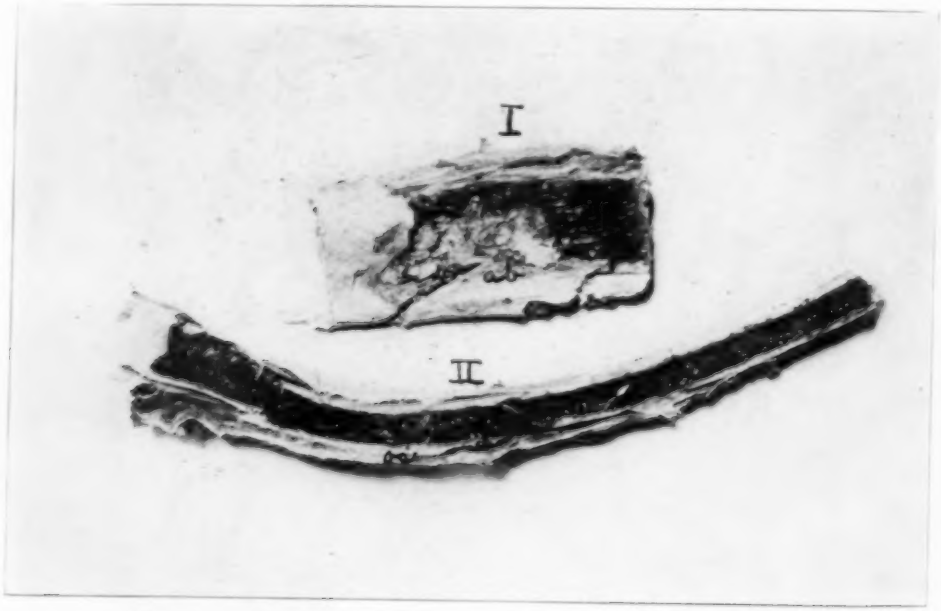

Fig. 2.—I, blastomycotic abscess (*ab*) of rib, part of which has been cut away. Subcutaneous abscesses secondary to lesions of the ribs have been common features in most of the cases. II, section of a rib showing blastomycotic osteomyelitis most marked at *os*. The blood of this patient contained many myelocytes.

mottled with red. The centers of the lobules were dark-red, the peripheries light yellow. In sections an angioma, 1.5 cm. (⅝ inch) in diameter, and a small adenoma were found, but no nodules or abscesses were discovered.

The spleen weighed 100 gm. (3½ ounces). The capsule was somewhat thickened, the consistency firm. On section the tissue was pale and the trabeculae and lymphoid tissue seemed increased. Numerous blastomycetes were obtained from a few small yellow areas, 1 mm. (1/25 inch) in diameter.

The kidneys together weighed 400 gm. (14 ounces). On section of the left kidney the cortex measuring 8 mm. (⅓ inch) rolled out beneath the capsule; the pyramids, from 16 to 18 mm. (2/5 in.) in length, were dark. The capsule stripped

readily, leaving a smooth surface. Beneath the capsule in the substance of the kidney were small yellow nodules from 1 to 2 mm. (1/25 to 1/12 inch) in diameter, quite solid and easily separated from the tissue. When one of these was crushed under a cover-glass in a 20 per cent. solution of sodium hydroxid, a number of blastomycetes were found. The right kidney corresponded to the left, except that the nodules described were more numerous, twelve being counted on the cut surface and beneath the capsule. The ureters were normal.

The adrenals were normal except for a few small yellow nodules which were saved for histological examination. The bladder was small, the walls thickened and the trabeculae prominent. The mucosa of the neck of the bladder and the posterior urethra were reddened, and on pressure yellow pus escaped from the ducts.

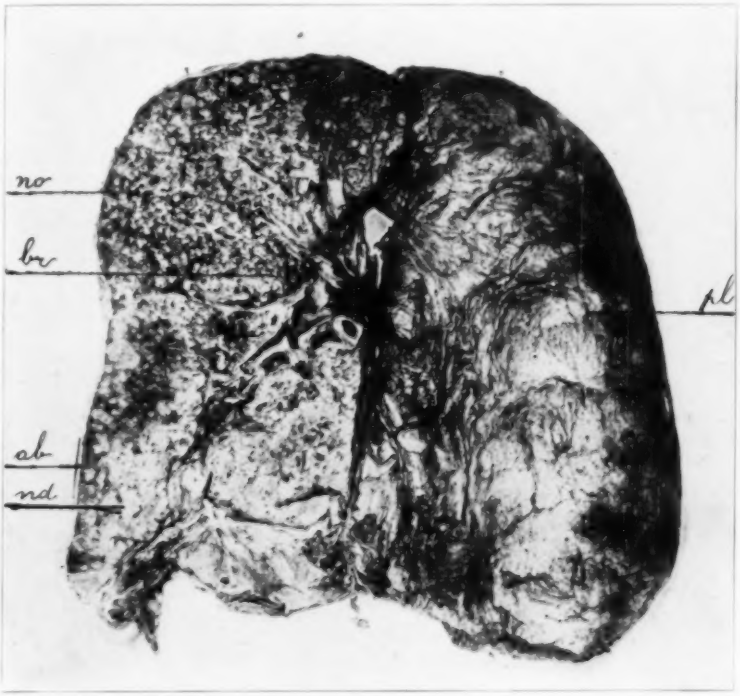

Fig. 3.—The right lung showing the thickened pleura (*pl*) and numerous nodes (*nd*) and nodules (*no*) on the cut surface. A small abscess (*ab*) was present between the pleural layers, and considerable fibrosis existed about the larger bronchi (*br*).

The prostate was enlarged and contained a fluctuating region in the left lobe. On section this lobe presented a central necrotic mass, with lines of the same material, or fine white nodules radiating to the capsule. The right lobe contained a few small abscesses. The seminal vesicles were distended with clear brown fluid. The testicles were atrophic, the vasa deferentia normal.

The brain weighed 1,400 gm. (3 pounds, 1½ ounces). No gross lesions were present externally. On section, in the cortex on the left side, near the middle of the sulcus between the parietal and occipital lobes, a small abscess 2 mm.

(1/12 inch) was exposed. Blastomycetes were demonstrated in the pus in this abscess. In the right hemisphere a small nodule was found in the temporal lobe, one in the parietal lobe and two in the occipital lobe. These were small, located in the cortex and usually at the margin of the white matter. In the right lobe of the cerebellum there was also a small nodule, and a second occurred in the left lobe as a white nodular mass with central degeneration from 1 to 4 mm. (1/25 to 1/6 inch) in diameter; this second lesion extended from near its internal surface to within ½ inch of the extreme lateral margin. Blastomycetes were also demonstrated in the necrotic material from this area. The spinal cord externally and on section presented no gross changes.

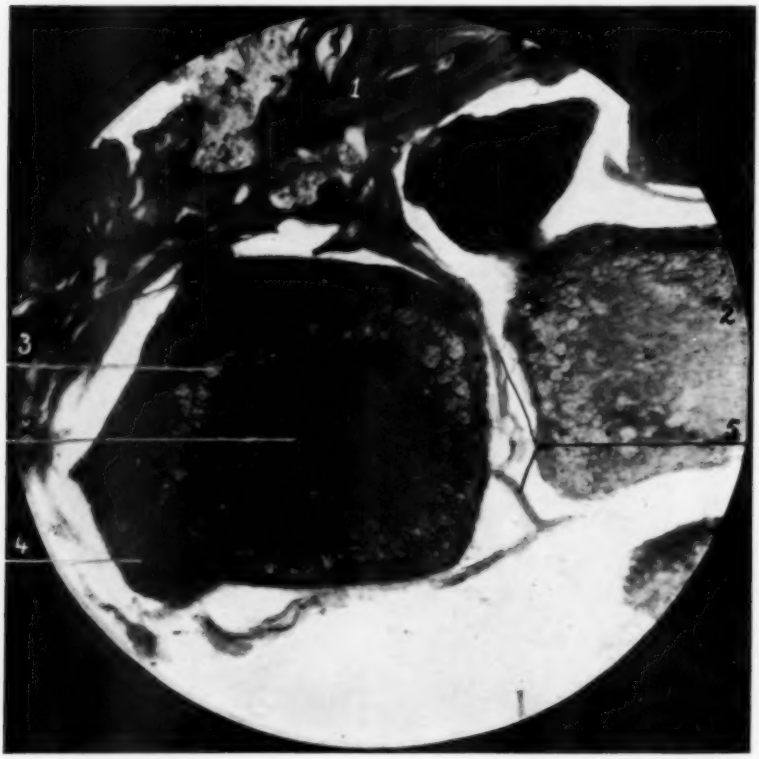

Fig. 4.—Section of the sternum showing infection of the bone marrow; 1, bone; 2, central zone of necrosis; 3, light areas representing clumps of blastomycetes; 4, peripheral border of unaffected marrow; 5, bony partitions which are sometimes absorbed, allowing the infected areas to become confluent, thus forming an abscess.

The histological examination failed to reveal any lesions characteristic of blastomycosis in the liver, adrenal testes or vasa deferentia. In the lungs there were found all degrees of coalescence of focal lesions, some so minute that they were little more than single alveoli, others large districts with more or less necrosis of their centers. As a rule they possessed the feature of blastomycotic

nodular lesions elsewhere in the character of the cellular exudate, giant-cells, organisms, etc. The fungi were very abundant. In the thickened pleura covering the right lung the so-called "miliary abscesses" were compressed and flattened out between the layers of fibrous tissue. In the spleen isolated organisms, some of them budding, were occasionally found in the sinuses at points where there was as yet no sign of tissue reaction, at other places minute focal lesions had developed about them. Many of the subcutaneous abscesses possessed no enveloping granulation tissue; especially was this true when the wall was formed by striped muscle. In the corium the inflammatory reaction was much more pronounced, and evidences of pressure were abundant. In some sections the fungi in the corium were so numerous as to resemble roughly fat areas with the high powers of the microscope.

The lesions in the brain were peculiar in the abundant necrosis, the appearance of bands of fibrous tissue between adjacent lesions probably due to pressure, and also in the angular bizarre giant-cells, which were relatively few. The lining of the right knee-joint was converted into granulation tissue resembling in a general way the margins of all large lesions; organisms were present but not numerous. The bone lesions differed perhaps most markedly from all the others in the comparatively little reaction of the tissue, necrosis being the predominant change (Fig. 4). In the prostate the change seemed confined to the glands which in the regions involved were more or less destroyed and converted into abscesses containing many organisms.

Bacteriologic Examination.—In addition to the cultures obtained during life, material was taken at necropsy from the knee-joint and the abscesses of the spleen, pleura and prostate. Pure cultures were obtained from the first three mentioned and a mixed culture from the prostate. The organisms were demonstrated in smears of material taken from the nodules of the kidney and the abscesses in the brain and rib. All the cultures obtained from pus and necrotic material appeared to be similar, but that obtained from the blood showed a few differences. A detailed comparative study of these is included with that of other organisms in the general summary.

A CASE OF SYSTEMIC BLASTOMYCOSIS

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CASE XX (2).—*History.*—J. S., aged 39, a Polish laborer, was admitted May 14, 1907, to the service of Dr. Heinick with the following history: The patient states that his present trouble began three months ago with severe pain in the right half of the head and face, most marked, however, over the malar prominence. This continued without remission until a month ago, at which time he began to experience pain in the right hip and knee. The latter became much swollen, and so painful that walking or standing was prevented.

A week later, pain was felt in the anterior part of the chest and in both shoulders, especially on inspiration or movements of the shoulders. Two weeks ago the left wrist became tender and swollen. A slight cough, present since the onset, has been more marked during the last two months, with blood occasionally in the sputum. The power of sight in the right eye gradually diminished, and at present the patient cannot recognize small objects a few feet distant. Although the appetite remained good he lost about 20 pounds. He also states that previous to this illness he had been strong and healthy. He is married and has five children. Venereal infection is denied. For the past four years he was engaged in the scrubbing and dusting of Pullman cars.

Examination.—The following points were noted in the examination: The patient is of medium stature, extremely emaciated and appears to suffer much pain even on slight movement. Beneath the scalp, over the vertex of the skull, is a tender fluctuating mass an inch in diameter. The conjunctiva of the right eye is red and edematous. Dulness is obtained by percussion over the upper lobe of the right lung anteriorly, and over the angle of the scapula posteriorly. On auscultation tubular breath-sounds and bronchophony are heard over the apex in front, but no râles are present. Over this dull area posteriorly the breath and voice sounds are diminished, but a few subcrepitant râles can be heard. The left lung appears to be normal. The heart is rapid but no changes can be demonstrated. Nothing of importance was found in connection with the abdomen or its viscera.

The right hip, knee and sternoclavicular joints are red, swollen and painful on motion. Fluctuation can be obtained over the knee. The right great toe is also swollen, and contains an abscess which has ruptured, discharging thick blood-stained pus. Scattered rather symmetrically over the body are fourteen deep and subcutaneous abscesses, varying in size from 1 to 5 cm. in diameter. These are distributed as follows: three in each arm, two over the chest and abdomen and six in the lower extremities. There are also pustular cutaneous lesions distributed on the right side of the nose, right cheek, left arm and both legs.

The temperature on admission was 101 F. The subsequent course of the disease was characterized by morning remissions of temperature to 98 or 99 F., and evening elevations to 101 or 102, associated with profuse sweats. This continued until the last week of illness, when the temperature became irregular and did not register much over 100 F. until the day of the patient's death, June 20. The pulse varied between 90 and 120 beats per minute until the last ten days, when it continued quite regularly between 120 and 140 per minute. The respirations averaged 26 per minute, becoming somewhat more rapid during the height of the fever. On June 15 a sudden change in the patient's condition was noted, the respirations becoming labored, rising to 60 per minute. He became cyanotic and complained of pain in the cardiac region, and for the next five days the respiration ranged between 44 and 56.

Up to this time the patient had manifested but few symptoms. Cough was of rare occurrence, and expectoration was so scanty that material for examination was obtained with difficulty. No organisms were found in that examined, but they were present in the mucus removed from the larynx at the necropsy. No tubercle bacilli were found. The abscesses increased in size and number, and were associated with great pain, especially on motion. A number of these were incised, and thick bloody pus was evacuated.

Diagnosis, Treatment and Course.—The diagnosis of blastomycosis was established June 10 by the demonstration of blastomycetes in the pus and their growth on culture mediums. Prior to this the patient was given a preparation of iron, quinin and strychnin as a tonic, and morphin, ¼ grain, from one to four times a day for the pain. On June 17, three days before death, he was given potassium iodid, 15 grains, and copper sulphate, ¼ grain, three times a day, without, however, any beneficial effect.

The majority of the abscesses which were incised continued to discharge profusely, and in the pus of a few of these the organisms could not be found. A note relative to an examination made on June 17 of the condition of the eye is as follows: "The conjunctivae of both eyes are much congested, and a purulent discharge is present. The cornea of the right eye is opaque, the pupil dilated and irregular, and the iris clouded and adherent in its right lower quadrant. The vessels leading to this region are engorged. These results were corroborated by Dr. Brown Pusey.

Two crusted ulcers were present at this time over the left eyebrow, three about the right shoulder, two on the right knee, three on the left knee and two on the left buttock, in addition to the lesions described previously, which had since become ulcerated. A majority of these presented the papillomatous appearance characteristic of cutaneous blastomycosis. It was noted that the abscesses which were not opened increased in size, and the left knee was also much swollen, and fluctuation could be determined.

Both jugular veins were dilated, the left one measuring an inch in diameter, the right forming a globular mass over 2 inches in diameter. No pulsation could be determined, but the veins became much distended during inspiration. The area of cardiac dulness was not much enlarged. The heart sounds were obscured by the rapid respirations. The lungs presented an impaired resonance in front with dulness to flatness behind. On auscultation anteriorly the breath sounds were harsh in character and a few coarse râles could be heard at the apex. On the sides the breathing was tubular in character, becoming distant and indistinct posteriorly.

A number of attempts to obtain cultures from the blood were made without success, and an estimation of the leukocytes made early in the course showed no increase. No noteworthy changes in the urine were found. The patient died of exhaustion as previously stated, on June 20, four months after the illness began.

Post-Mortem Examination.—Through the courtesy of Dr. W. H. Hunter, coroner's physician, the following data were obtained: The body was extremely emaciated and presented the numerous cutaneous lesions and the superficial and deep abscesses previously described. The latter were very extensive and contained a thick yellow or brown pus. The walls were made of adjacent tissues, and no lining membrane could be observed, except in those cases in which the abscesses had been incised and secondary infection had taken place.

An abscess 2 inches in diameter was present beneath the scalp, on the left side at the vertex. It communicated with a region of softening in the parietal bone an inch in diameter involving almost its entire thickness. An irregular perforation, 8 mm. in diameter, existed in the inner table exposing the dura mater, the surface of which was rough and necrotic.

The first rib contained an abscess near its junction with the sternum. The bone here had been destroyed, and an opening in the periosteum communicated with a collection of pus beneath the bulging skin. Similar abscesses were present in the third, fifth and sixth ribs on the right side. The right knee-joint was much

enlarged and its synovial cavity contained a large quantity of pus, the crucial ligaments were destroyed, and slight erosions existed at their points of attachment. The articular surfaces were otherwise smooth. The left knee also contained a large quantity of pus. The left elbow was much swollen. The olecranon had been fractured, and the head of the ulna was completely disorganized. An abscess extended from this point into the forearm along the ulna to the wrist. The terminal phalanx of the right great toe had been destroyed, and erosion with abscess formation in the small bones of the left wrist was present. Still another collection of pus was found over the sternum communicating with an abscess in the sternum. The latter occupied the greater portion of the right

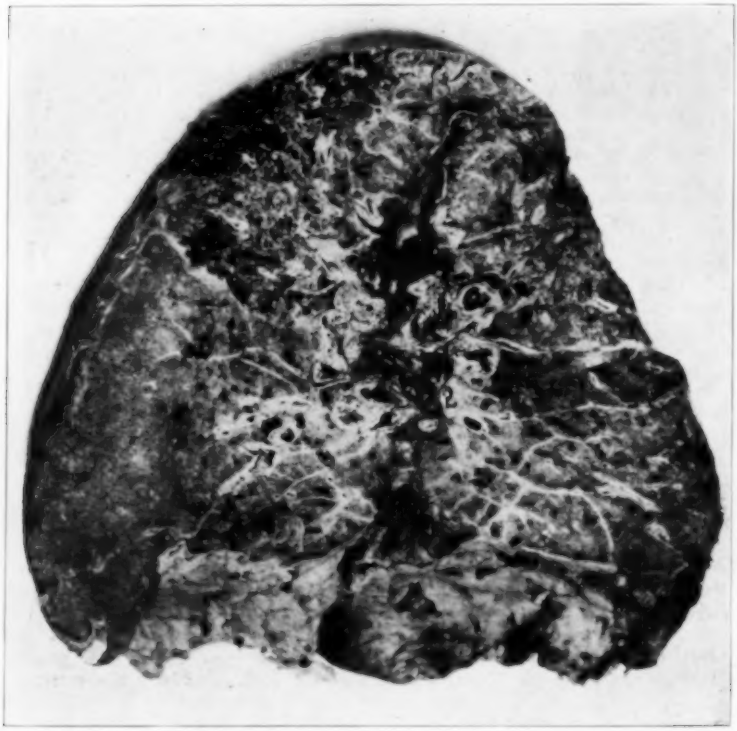

Fig. 1.—Right lung. The infection here was so extensive that the lung was almost solidified, and presented an appearance not unlike that of an organized pneumonia. Blastomycotic nodules can be seen with difficulty, but the organisms were very numerous in the microscopic sections.

half of the manubrium, and extended to the periosteum of the posterior surface. On section the infected bone about the abscess was slightly yellow, and considerably softer than normal.

The right eye showed the changes noted in the examination made a few days before death. The tonsils were enlarged and the crypts contained a caseous material in which no blastomycetes were found. The cervical, mediastinal and peribronchial lymph-nodes were enlarged.

Both pleural cavities were obliterated anteriorly by fibrous adhesions, which were especially firm at the apex (right) and opposite an abscess in the third rib. The tissues about the apex were so involved in the cicatrical mass that the right jugular vein was constricted. Above this point the vessel was dilated to the extent that its lumen measured 1½ inches in diameter. Posteriorly, on both sides, the chest contained a large amount of turbid fluid, and the pleurae were covered with a thin fibrinous exudate.

The right lung weighed 960 gm., was quite firm and did not collapse. Slight crepitation could be obtained over the greater portion. The posterior surface was covered with a thick coat of fibrin, and anteriorly fibrous tags were present. The interlobar fissures were obliterated. On section the upper lobe was firm, and dense white bands of connective tissue radiated from a cicatricial region torn from

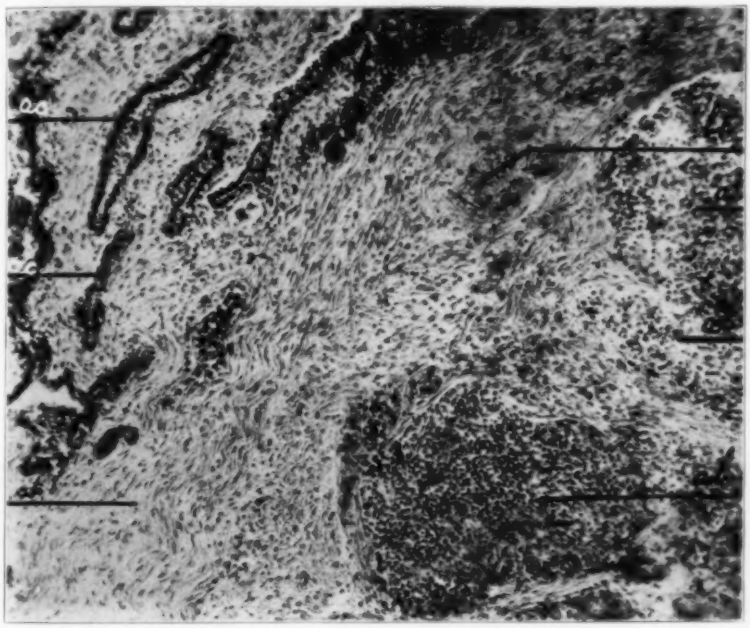

Fig. 2.—Photomicrograph of blastomycotic abscesses of the prostate gland: *ac*, normal acini; *ab*, abscesses in infected acini; *st*, fibrous stroma; *bl*, a small clump of blastomycetes.

the third rib, to which it was adherent. The intervening tissue was quite solid and contained very little air. Numerous small white nodules were scattered throughout, and a few small caseous areas were present, the material from which contained many blastomycetes. The middle and lower lobes on section showed an increase of the interlobular connective tissue. The greater part of the lung was firm, smooth and translucent, with irregular intervening regions of apparently normal lung, from which a frothy fluid could be expressed. No air was present in the solid portions. Many small white nodules were scattered throughout the lung (Fig. 1). The left lung weighed 700 gm., and presented a small amount

of fibrin on its posterior surface. It crepitated feebly throughout, and on section the appearance was similar to that of the middle lobe of the right lung. The general appearance was that of an organized pneumonia. The small bronchi were filled with a thick purulent material in which blastomycetes were demonstrated. The pericardial cavity contained 3 ounces of turbid fluid, and the lining membrane was slightly roughened. There was a slight thickening of the mitral valves. No lesions were visible in numerous sections of the musculature.

The stomach and intestines possessed no changes of importance, except that Peyer's patches were pigmented and reticulated. The mesenteric lymph-nodes were considerably enlarged. The liver and kidneys were opaque and gray on cut sur-

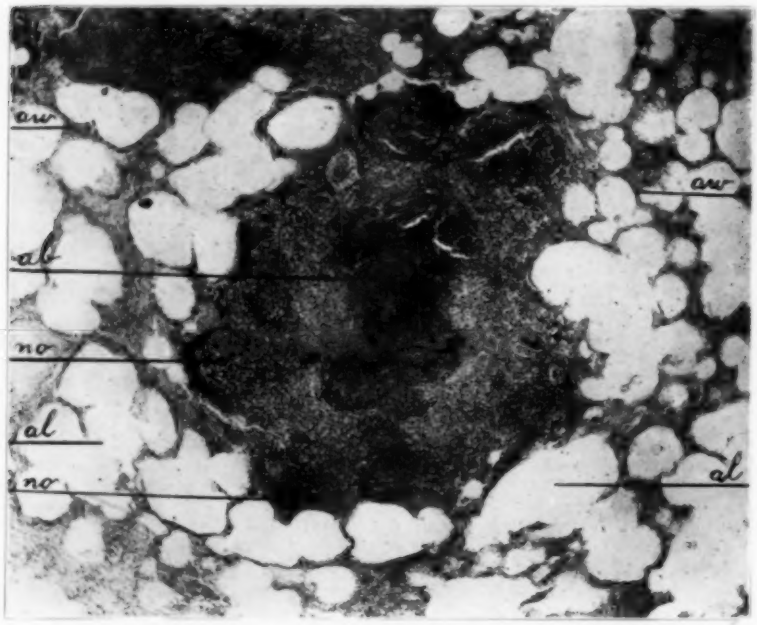

Fig. 3.—Photomicrograph of a fairly typical blastomycotic lesion of the lung: *ab*, necrotic center of a small node made up of *no*, confluent nodules; *al*, alveoli; *aw*, alveolar walls.

faces. The spleen was normal. These viscera were carefully examined for blastomycotic lesions, and a number were found in the kidneys. The adrenals, bladder, testicles, pancreas, vas deferens and seminal vesicles were normal. The prostate was enlarged, and on section a small abscess 5 mm. in diameter was exposed in the lobe. The glandular structure of the left side showed slight changes.

No nodules were found in the left lobe of the cerebrum, and the remainder of the brain was not obtained for examination.

Anatomical Diagnosis.—Serofibrinous pleuritis and pericarditis; miliary blastomycotic nodules of the lungs, pleurae and kidneys; multiple blastomycotic abscesses of the lungs and prostate and the osseous, muscular and subcutaneous

tissues; blastomycotic ulcers of the skin; blastomycosis of the right eye;[1] purulent bronchitis; parenchymatous degeneration of the kidneys and liver; fibroid induration of the lungs; fibrous pleuritis.

Histologic Examination.—No changes of importance were found in the stomach, intestine, mesenteric or tracheobronchial lymph-nodes. The liver was moderately fatty; in sections of the spleen occasional isolated blastomycetes were found without changes in the surrounding tissues. In some of the kidney sections blastomycotic abscesses, the size of a low-power field (Obj. iii, Ocular ii, Leitz) occurred in the cortex and the usually rather abundant giant-cells containing organisms were scattered about the abscess margins. The heart-muscle cells were atrophied, and on the epicardium and beneath it the changes ordinarily present in slight fibrinous inflammations were found; nothing, however, was found to indicate the essentially blastomycotic nature of the pericarditis.[2]

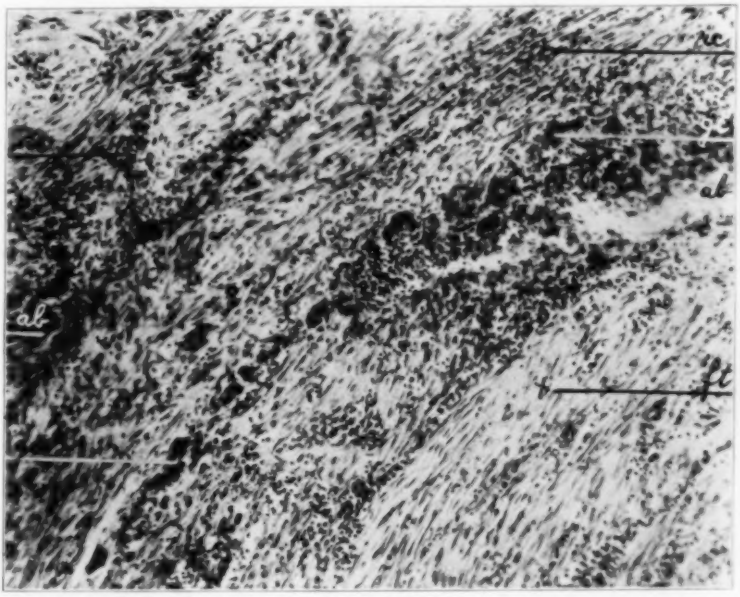

Fig. 4.—Photomicrograph of a section of thickened pleura: *ft*, fibrous tissue; *ab*, small abscess formations; *gc*, giant-cells; *rc*, areas of round-cell infiltration.

In sections from the sternum at some distance from the abscess, the changes were limited to the periosteum, which was thickened and under which were col-

1. Owing to the fact that the lesions of the right eye developed during the course of the illness, considerable speculation was aroused as to its nature. Unfortunately permission to remove the eye was not obtained. The eyeball was therefore rotated, a sterile puncture made and a portion of the vitreous humor removed. From this, a pure culture of blastomycetes was obtained. In view of this result the assumption that the lesion was one of metastatic blastomycosis is perhaps not far-fetched. Supporting this view are the facts that pain noted about the region of this eye and disturbance of vision, indicating its involvement, were among the first symptoms.

2. See bacteriological examination.

lections of partially necrotic leukocytes and many organisms. The marrow appeared but little altered.

In the sections of the cutaneous and subcutaneous lesions the changes in some were much like those described for chronic blastomycotic dermatitis, to which there were added the extensive regions of destruction produced by the deeper lying suppuration; in other sections the process was more limited to the subcutaneous tissues. Except for the presence of the focal lesions so characteristic of this disease, which were scattered about the subcutaneous abscesses, the inflammatory process possessed the features of almost any chronic suppuration.

In the prostate the great number of organisms filling some of the acini was indeed remarkable (Fig. 2). The glands seemed dilated by the organisms alone. From such accumulations accompanied by little alteration in the surrounding gland tissue there were all degrees of change for the extensive destruction noted in the gross examination. Focal lesions, the minute blastomycotic "abscesses" with their peripherally located giant-cells, were conspicuously absent in the prostate sections examined. The changes in the lungs (Fig. 3) varied in the different regions examined from recently produced bronchopneumonia to rather marked fibrosis. In both, as well as in the greatly thickened pleura, the "abscesses" were scattered about, although in the pleura these disseminated lesions with organisms were flattened out between the dense masses of fibrous tissue. (Fig. 4.)

Bacteriologoy.—Pure cultures of blastomycetes were obtained from the pus of various abscesses, from time to time during life. At the post-mortem examination, medium was inoculated or material taken for inoculation from the blood, bile, pleural, pericardial and peritoneal fluids, the vitreous humor of the right eye and pus from the knee-joint, and the abscesses of the neck and prostate gland.

Streptococci were grown from the blood, pleural and peritoneal fluids and the pus of the knee-joint. The blastomycetes were isolated culturally from the pericardial and pleural fluids, vitreous humor of the eye and the prostatic abscess. The results of study of these organisms are mentioned elsewhere in this report. The presence of the streptococci was regarded as the result of a terminal infection inasmuch as there were clinical manifestations of such a condition during the few days prior to the patient's death. The failure to recover any organisms culturally from the pus of the neck and the knee-joint would indicate possibly that with and without secondary infection the blastomycetes may die or disappear from the pus of the abscesses in which they had previously been demonstrated.

Thanks are hereby extended to Dr. Heinick, attending physician, for his permission to report the case.

A CASE OF SYSTEMIC BLASTOMYCOSIS

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CASE XXI (3).—*History.*—M. C., Italian, aged 17, was admitted to the Cook County Hospital, May 20, 1907, to the service of Dr. Goodkind, with the following history: His illness began five months ago with the appearance on the anterior surface of the middle of the right thigh of an abscess which ruptured and discharged a thick, fetid, dark-brown pus. A papillomatous crust formed subsequently at the site of the abscess. There was at the same time a small abscess near this which healed in a few days. Two months later a sharp stabbing pain occurred in the right knee. Motion soon became restricted and in two weeks a swelling of the joint appeared. This gradually increased so that in two months the knee was twice its normal size. It remained in this condition until the time of his admission to the hospital. One month after the onset of the pain in the right knee, the left knee became similarly involved, but the pain and swelling were less severe. The right ankle also became affected, but the process did not progress and at present (the time of his admission) shows no signs of inflammation. Marked swelling, accompanied by pain and tenderness, occurred successively in the left ankle, both elbows, left wrist and the first metacarpophalangeal joint of the left hand. A small papule developed in the left eyebrow one month after the commencement of the joint troubles, and since then similar lesions have appeared on other parts of the face and head. (Fig. 1.)

The patient was born in Italy and from the age of 10 was engaged in hard manual labor on a farm. Four years ago he came to the United States and has worked at intervals as an organ-grinder and helper in a machine shop, until the onset of the present illness. He lived in the congested Italian district on the west side of Chicago, and his living quarters were unhygienic in the extreme. The rooms themselves were dry at the time of investigation (summer) but the basement in which the closets were located was wet, and decomposing feces and wood were found in many places. His health had always been good and he denied venereal infection. The family history was unimportant except that his father died two years ago after an illness of two months during which time he coughed frequently, often expectorating blood.

First Admittance to Hospital.—When admitted to the hospital, on account of the multiple arthritis, the diagnosis of chronic rheumatism was made. The course of the disease, however, during the subsequent two months, led to the consideration of tuberculosis and syphilis as possible explanations of the symptoms, and the latter was favored because of an interpretation given to the appearance of the bones of a roentgenogram of the hand. The subsequent development of an abscess beneath the scalp, and its characteristics resembling those encountered in other cases of blastomycosis, led to the examination of aspirated pus and the discovery of the organisms. The patient now was anemic and emaciated; seemed quite comfortable and complained of pain and stiffness of the joints. The pulse was 108; temperature 101.8 F.; respirations 28. On the face were a number of small oval, indurated, purplish ulcers, their edges being fairly regular and rounded margins sloping outward to the skin around them. The largest of these situated above the right eye and measured 6 by 20 mm. Other similar lesions in various stages of involution were present on the back of the neck, scalp, arms, thighs and left ankle. An oval "rice-paper" scar was present on the upper part of the right thigh, and below this a fistulous opening discharged bloody pus. It was surrounded by an oval area of indolent

granulation tissue and represented the site of rupture of the first abscess which appeared. Beneath the scalp three small abscesses were found; one of these was more deeply situated and seemed to be connected with the bone.

The eyes, ears, nose and neck were normal. The chest was negative on inspection except over the tenth rib in the posterior axillary line on the left side, where there was a soft rounded swelling the size of a hazelnut, and evidently attached to the rib. Resonance was impaired over both apices in front and

Fig. 1.—M. C., photographed a few days before death. Note the cutaneous lesions on the left cheek and right hand, the swollen and ulcerated condition of the left elbow, and the marked swelling of the knees.

behind. The respiratory murmur was roughened and expiration prolonged. No râles were heard anywhere. Posteriorly below the left scapula, resonance was impaired and the voice and breath-sounds slightly diminished. A faint systolic murmur over the pulmonic area and a slight enlargement of the liver were the only alterations in the further examination of the chest, abdomen and genitalia.

The muscles of the extremities were atrophied. Both elbows, the right wrist, both knees and the left ankle were swollen and tender, and motion was restricted and painful. There were in the right hand two small abscesses involving the first metacarpophalangeal joint and the middle phalanx of the fourth finger. A sinus on the palmar surface of the fourth finger communicated with the last-named abscess and discharged a thick brown pus. The left wrist was tender, and extending from an abscess in the first metacarpophalangeal joint were two sinuses, one dorsal and one palmar, each discharging a thick yellow pus.

There were no disturbances referable to the nervous system. The superficial cervical and epitrochlear lymph-nodes were slightly enlarged.

The urine was amber, clear, acid in reaction, specific gravity 1.018, and contained no albumin, sugar or casts. No blastomycetes were found in the urine obtained after massage of the prostate. Examination of the feces failed to show anything of importance.

The blood contained 3,800,000 red cells per cubic millimeter; 9,600 white cells and 65 per cent. hemoglobin (von Fleischl). A stained specimen showed slight poikilocytosis but no nucleated red cells. The differential white count was as follows: polymorphonuclear neutrophils, 55 per cent.; small lymphocytes 32 per cent.; large lymphocytes, 11 per cent.; eosinophils 2 per cent. No cultures were obtained from the blood in several attempts.

The course of the disease was slow and marked by several remissions and exacerbations. The pulse ranged from 80 to 120; the temperature was highest in the evening and varied between 98 and 103.6 F. After June 22, when the diagnosis was established, the patient was given increasing doses of potassium iodid, tonics and fresh air treatment and rapidly improved. The pain in the joints disappeared and he left the hospital July 8 and resumed his occupation, organ-grinder.

Second Admittance to Hospital.—Ten days later he returned to the hospital with a marked aggravation of all his joint-symptoms. He coughed much, expectorating slight amounts of mucoid material, and suffered greatly from pain in the joints; the pulse was 84; temperature 100.8; respirations 24. The right ankle, which was normal previously, was swollen and tender, and two new abscesses had appeared on the ulnar side of the right wrist and on the tarsal surface of the left wrist extending into the hand.

The physical signs in the lungs were also more pronounced, but no râles were heard. Administration of potassium iodid was resumed with no improvement for about eight days. Many new abscesses appeared successively on the hands and feet, and the temperature ranged up to 103.4 F. Copper sulphate was now given internally in ¼ grain doses three times a day and the hands and feet, in which were many discharging abscesses, were dressed with hot 0.5 per cent. solution of copper sulphate. The patient again improved, the cough subsided; the abscesses healed and the joints became less painful.

Repeated examinations of the sputum were made for the tubercle bacillus and blastomycetes with negative results until August 5, when budding blastomycetes were found. The improvement continued and the patient gained in weight and strength. The temperature did not rise above 99 F. after August 11. All the fistulas closed and he left the hospital August 17 in good condition, there being only slight limitation of motion in the elbows and knees. At the time of discharge 150 grains of potassium iodid three times a day and ½ grain of copper sulphate three times a day were being given.

Third Admittance to Hospital.—The patient again applied for admission to the hospital Dec. 12, 1907, and was assigned to the service of Dr. Mix and afterward transferred to the surgical service of Dr. Ryerson. During the second furlough of four months he suffered many hardships. He had taken no medicine, and had tried to return to Italy, but the officials at New York refused him passage and he was forced to sell papers on the streets in order to obtain food. He entered the hospital much emaciated and in a very weak condition,

with an exacerbation of all his old lesions and some new ones. The pulse ranged from 90 to 130, temperature 98.6 to 103.6 F., respirations 22 to 30. There was a general adenopathy, especially noticeable in the axillary, cervical and inguinal regions. Large abscesses involving both knees, wrists, elbows and ankles were present, the one about the right knee being very large and fluctuating and extending half way up the thigh. The others had ruptured and discharged a thick yellow pus. He suffered excruciating pain on movement of any of these joints. The ulcers of the skin were larger, and new lesions were present on the lip and the back of the neck. Impaired resonance and harsh breathing obtained over the apices of both lungs.

Increasing doses of potassium iodid and a nutritious diet were again administered, but the patient became weaker despite treatment and died Jan. 16, 1908.

Early in the course of the disease, Bier's passive congestion treatment was used, but it seemed to do little good. As soon as the patient was able to leave his bed he spent nine hours a day in the sunshine and open air.

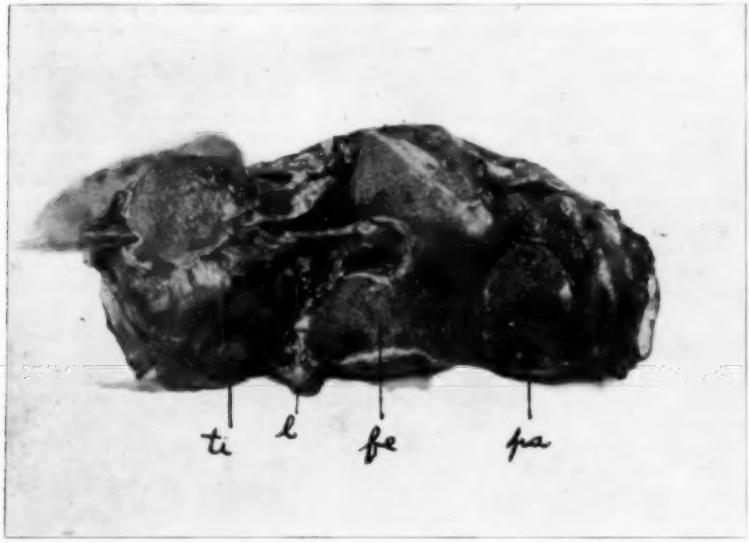

Fig. 2.—Articular surfaces of left knee: *ti*, eroded surface of head of tibia; *fe*, lower end of femur on which only a portion of the articular cartilage remains; *pa*, patella, in which are two abscesses, the openings of which are exposed; *l*, articular ligaments which were so disorganized that subluxation occurred.

Necropsy.—A post-mortem examination (Dr. Stober) was held two days after death and the following is the anatomical diagnosis: indurated blastomycotic bronchopneumonia of the left lung; blastomycosis of bones, subcutaneous and cutaneous tisues, pons Varioli, inguinal and axillary lymph-nodes; acute vegetative mitral endocarditis; fatty liver; parenchymatous degeneration of the kidneys; fibrous pleuritis; hyperplasia of the lymphoid tissue of the ileum; edema of the lungs; hydropericardium; atrophy of the heart, pancreas and testicles; emaciation and anemia.

The body is that of an extremely emaciated young man. Numerous cutaneous lesions, abscesses and fistulas are present, the majority of which have been described in the clinical report. Both knees are markedly swollen and the

skin covering them contains several ulcers and discharging fistulas. A posterior subluxation has occurred in the right knee, and the same condition can be produced in the left knee. The joint-cavities contain a large amount of bloody pus, the periarticular tissues are disorganized, the ligaments destroyed and the cartilages have disappeared, exposing the rough granular surface of the bones (Fig. 2.) About these joints large communicating abscesses exist; the one above the left knee extends the whole length of the thigh and contains nearly a quart of pus. Another above the right knee is about half as large. Discharging abscesses involving the elbows and the small bones of the feet are also present. The articular structures of the latter have been practically destroyed. There are abscesses communicating with the lymph-nodes in both groins and in the right axilla. The lymph-nodes of the left axilla are enlarged and pink on section.

The pleural cavities contain about 2 ounces of a clear yellow fluid, with slight fibrous adhesions about the apices and also to the diaphragm on the left side. The pericardial cavity contains 4 ounces of a clear yellow fluid.

The lungs weigh 620 gm. Both crepitate freely and do not collapse. The left lung on section is mottled light gray and on pressure exudes a slight amount of frothy fluid. In the extreme lower margin of the lower lobe and externally is a region of induration roughly 5 by 1 cm. in diameter, somewhat circular in outline and directed toward the root of the lung, where it is continuous with a similarly indurated tissue behind the main bronchus, in which there are several yellow regions of necrosis (Fig. 3). The pleurae overlying the consolidated lung tissue next the diaphragm is thickened and binds the lung to that structure. The lung beneath contains numerous small blood-vessels and bronchi surrounded by firm tissue heavily pigmented with coal-dust. The pericardium is generally adherent to the left lung. The remainder of this lung as well as the right lung is unchanged. The tracheo-bronchial lymph-nodes contain large amounts of coal pigment and are slightly enlarged.

The tongue is normal. The tonsils are small and from their crypts a purulent material is expressed. The esophagus is smooth; the trachea and larynx are slightly hyperemic and contain mucopus.

The heart weighs 240 gm. The pulmonary tricuspid and aortic valves are normal. The mitral valve is thickened and on the edge of both cusps are fine warty vegetations the largest of which measures 1 mm. in height. The heart-muscle is pale; the left ventricle wall measures 5 mm. in thickness, the right 2 mm. The aorta and coronary vessels are normal. The liver weighs 1,400 gm. Its surface shows the imprint of the ribs. On section the tissue appears somewhat opaque and light yellow. The spleen weighs 200 gm. Its capsule is thickened, its consistency firm, the cut section brown, and there is an increase in the connective tissue. No microscopic nodules are present.

The brain weighs 1,600 gm. It is normal externally. In numerous sections, one blastomycotic nodule is found in the pons a few millimeters below the ventral surface.

The kidneys weigh 280 gm. On section the kidney substance bulges; it is a grayish-yellow; the cortex is increased in thickness and the capsule strips readily, leaving a smooth surface.

The testicles are small, and sections expose an increase in connective tissue. The bladder is small and contains a small amount of turbid urine. The rugae are fairly prominent; the posterior urethra is congested and slightly granular. The prostate and seminal vesicles are normal. The pancreas is firm and small. The mucous membrane of the stomach is thin, and small ecchymoses are present about the pyloric region. The intestines are normal.

The left leg was amputated through the thigh for a more detailed examination. A small opening into the knee-joint from an abscess in the internal condyle was found, as well as several small regions of softening in the cancellous bone of the patella. The abscess in the condyle was 3 cm. in diameter and the passage into the joint one-third as large. The bone about the

abscess as well as that just beneath the articular cartilages of both tibia and femur was soft and diffusely yellow; on crushing a semipurulent fluid was obtained (Fig. 4). On the antero-internal surface of the tibia at the junction of the upper and middle thirds an opening 5 mm. in diameter was found passing through a raised bony and shell-like periosteum under which was a small abscess not connected with the marrow cavity. The epiphyses of the lower end

Fig. 3.—Section through the lower lobe of left lung: *fi*, fibroid area representing healing blastomycotic lesions; *pl*, thickened pleura adherent to the diaphragm.

of the tibia and fibula also contained small yellow softened regions communicating with abscesses over both malleoli which had ruptured externally (Fig. 5), the one over the external malleolus continuous with an abscess extending beneath the Achilles tendon. Occupying the greater part of the dorsum of the foot was a sharply demarcated region of necrosis, and the tissues bordering this were

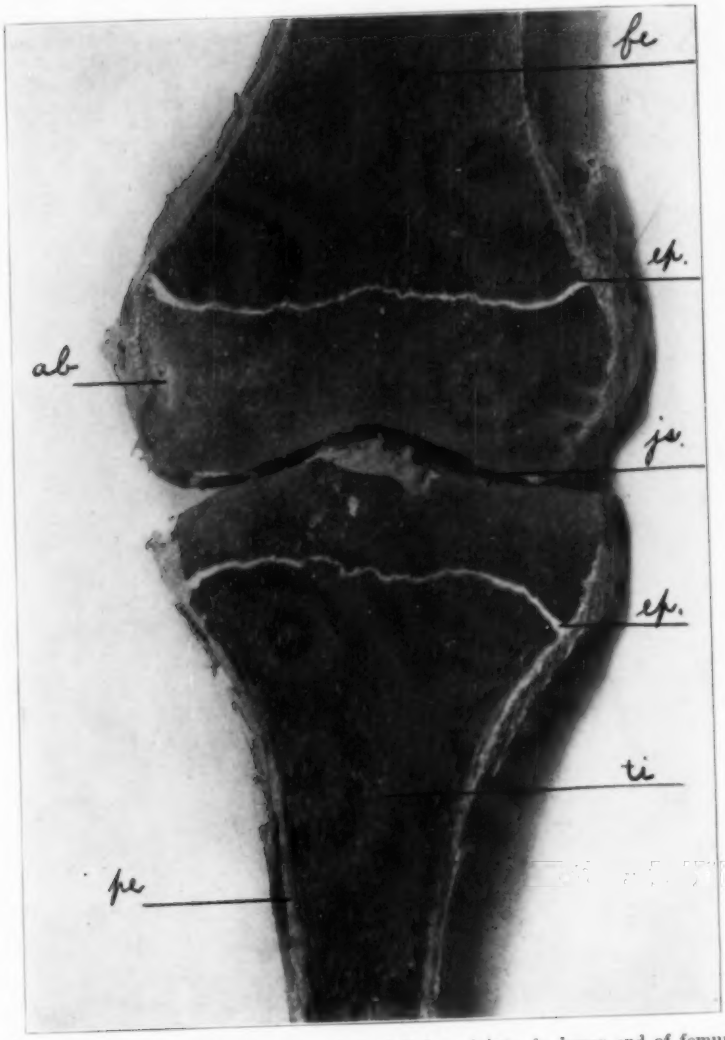

Fig. 4.—A longitudinal section of the left knee-joint: *fe*, lower end of femur; *ti*, upper end of tibia; *ep*, epiphyseal line; *js*, eroded joint surfaces; the light color of the adjacent bone represents the extent of the blastomycotic process; *pe*, healed periostitis; *ab*, abscess in epiphysis which communicated with the joint.

without evidence of reaction. In this region the unchanged extensor tendons lay bare, and beneath were the fragments resulting from the disorganization of several of the tarsal and portions of the metatarsal bones (Fig. 6). In the pus of the joint cavities, bone abscesses and adjacent soft cancellous marrow were to be found many round and budding blastomycetes, some of which possessed capsules of unusual thickness.

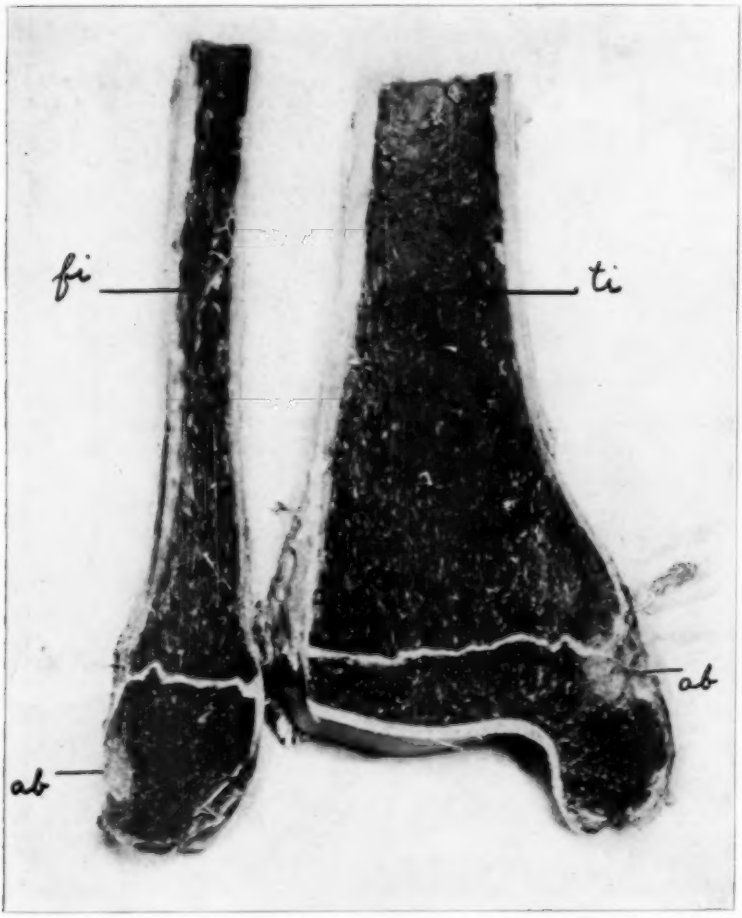

Fig. 5.—Longitudinal section through tibia (*ti*) and fibula (*fi*) with abscesses (*ab*) in the epiphyses.

Histology.—In sections of the indurated region in the left lung, compressed and distorted bronchi were found surrounded by masses of adventitious fibrous tissue; one of these bronchi contained enormous numbers of blastomycetes. Several of the minute so-called abscesses with organisms and the other features of such blastomycotic local lesions were scattered about in this fibrous tissue. The

other alterations were those commonly encountered about regions of chronic disease in the lungs.

The changes in the bones were of special interest on account of the extensive necrosis. Sections were studied from the abscesses in the patella, fibula, femur and tibia, and the alterations were quite similar. The centers of small abscesses and the tissue near the surfaces of such as had discharged their contents were made up of disorganized and necrotic bone, leukocytes and red cells. In the sections from the yellow and soft cancellous bone beneath the articular cartilages

Fig. 6.—Ulcerations communicating with blastomycotic abscesses in the metatarsus (*me*) and external malleolus (*em*). Muscles, bones and tendons have been exposed.

there was a diffuse necrosis for the depth indicated in the gross description, a necrosis evidently due to the rather regular extension into the head of the bone of the blastomycosis of the joint. This diffuse necrosis was difficult to explain by the coalescence of local lesions. In some sections zones of mononuclear leukocytes surrounded the necrotic tissue, but no evidences of granulation tissue about

these was found, and organisms occurred outside the lesions in the cavities of the marrow where but little change had taken place. Histological changes in accord with the gross description, both indicating the formation of new bone from the cambium, were found in the shell-like but perforated and imperfect outer wall of the abscess on the inner surface of the upper part of the tibia.

In the inguinal lymph-nodes not only were focal lesions present, such as have been repeatedly described in the tracheobronchial lymph-nodes, but also peripheral lymph sinuses were found crowded with organisms, evidently in the current since the adjacent tissues were without alterations. In the spleen, too, organisms were found; at one point a clump of fifteen or twenty, at another, budding forms and about them no evidences of tissue reaction. The lesion of the pons, 3 mm. from the ventral surface and approximately 1.5 mm. in diameter, contained numerous organisms and was apparently formed by the coalescence of more minute local lesions. The changes in sections of other tissues and organs conformed to the anatomic diagnosis.

Bacteriology.—The *Staphylococcus albus* and *aureus* were recovered from the blood, pleural fluid, bile and pus from the abscesses of the knee-joints, left inguinal and right axillary regions. Blastomycetes were demonstrated in the pus of the abscesses mentioned as well as in the necrotic material from numerous bone lesions, but were not obtained in culture. The failure to cultivate these organisms from material yielding cultures during life is not an infrequent post-mortem occurrence.

This report is of more than ordinary interest on account of the improvement which occurred during the first two periods in the hospital, and also because of the existence of relatively slight blastomycosis in the lungs at the time of death — the organisms having disappeared from the sputum some time previously and coincidentally with the fewer evidences of pulmonary alteration on physical examination — and the very extensive involvement of the subcutaneous tissues, bones and joints.

A CASE OF SYSTEMIC BLASTOMYCOSIS

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CASE XXII (4).—*History.*—The patient, C. T. S., entered the Cook County Hospital May 8, 1907, to the service of Dr. Ryerson. He complained at the time of dyspnea, pain in the right side of the chest, occasional night sweats, chills and fever. His right ankle was painful and swollen, and on the face and left side of the abdomen were cutaneous lesions which his physician had diagnosed and treated as lupus. The first of these to occur was a small papule over the eleventh rib on the left side, discovered accidentally in December, 1906, while scratching his body. This ulcerated and gradually increased in size until March, 1907, at which time it measured an inch in diameter, and was treated as lupus, without benefit. A similar lesion developed on the left side of the chin after the top of a small papule was cut off during shaving. A short time later another lesion occurred over the left eye, following the scratching of what the patient thought was an insect-bite. In January, 1907, he first noticed night sweats, and several months later a cough associated with bloody expectorations. In February he went to Arkansas, and while there suffered from chills and fever, which were relieved by quinin. At this time he also noticed a tenderness of the right external malleolus which later became painful and swollen, together with an abscess of the heel causing a gnawing pain at night and some soreness when the limb was first used in the morning.

The patient had been a clerk for three years. His previous illnesses were unimportant. His father died of gastric carcinoma at the age of 45. From May to November, 1906, he was engaged in dredging, during which time he slept in a cabin-boat, which he stated was quite damp at times. During June and July he slept with a man who was suffering from what he thought was consumption.

Examination.—At the time of admission the patient was poorly developed, considerably emaciated and very anemic. Crusted lesions were present above the left eye, on the left side of the chin and on the left side of the abdomen, and there were soft fluctuating abscesses on the left side of the neck and over the right external malleolus, the latter quite red and very painful on pressure. Examination of the lungs demonstrated dulness on percussion over the right upper lobe, increased transmission of whispered and spoken voice-sounds, and numerous small mucous râles. No dulness was obtained over the remainder of the right lung or over the left lung. Expiration, however, was prolonged, and the breath-sounds somewhat harsh in character. A few moist râles were heard over both bases. The heart action was strong and forcible, with accentuation of the aortic and pulmonary second sounds. The liver extended one finger's breadth below the costal arch; the spleen was not palpable. The urine was normal, save for an occasional hyaline cast. The temperature on the day after admission was 100 F.; pulse 76; respirations 22. On May 10 Dr. Ryerson made an incision into the swelling over the right external malleolus and considerable pus was evacuated. Extending through the periosteum to the epiphysis of the fibula a small sinus was found which from its appearance was considered tuberculous. It was enlarged, the cavity curetted, swabbed with tincture of iodin, and closed with a small drain. The abscess in the neck was also curetted and the region of supposed lupus on the side excised. The wounds closed by first intention, but infection in the external malleolus appeared several months later. On May 14, four days after the operation, a swelling appeared on the left side of the face and profuse night sweats occurred. Pain was felt in the right foot, especially at night,

and a week later the patient experienced sharp, severe pain over the lower part of right chest; this was increased by inspiration and continued for four days. The next few days he complained bitterly of pain in both ankles and the right wrist, and Bier's passive hyperemia treatment was tried for some time without, however, producing much benefit. On June 7, a fluctuating swelling appeared in the right forearm, and the patient complained of pain in the back between the shoulders.

Fig. 1.—Right lung, Case 22; *br*, bronchiectatic cavity in upper lobe which has undergone fibrosis; *mn*, miliary blastomycotic nodules in lower lobe; *pl*, thickened pleura in which nodules were also present.

Treatment and Course.—Up to this time the disease had been considered to be generalized tuberculosis. Iron, quinin and strychnin had been administered as tonics, and other remedies as indicated for the pain and insommia. Because a viscid bloody pus obtained on June 11 from an abscess over the left tibia possessed the characteristics of pus from the blastomycotic abscesses in other cases it was

examined with the result that numerous blastomycetes were found. Subsequently these organisms were cultivated in pure culture from various abscesses. From this time potassium iodid, 60 grains, and mercurial inunctions, 1 dram, were given daily. A month later the mercury was discontinued and ¼ grain of copper sulphate was given three times a day. During the next two months the disease was marked by progressive weakness, emaciation and pain in the affected parts, especially in the knee- and ankle-joints. The pain was quite constant and so severe that large doses of codein and later of morphin were required for its relief. The temperature ranged quite regularly between 99 F. in the morning and 102 in the evening. Occasional sweats were noted. The pulse varied from 80 to 130 beats per minute, the respirations from 20 to 26. Toward the end the patient was quite irritable, and at times refused both food and medicine.

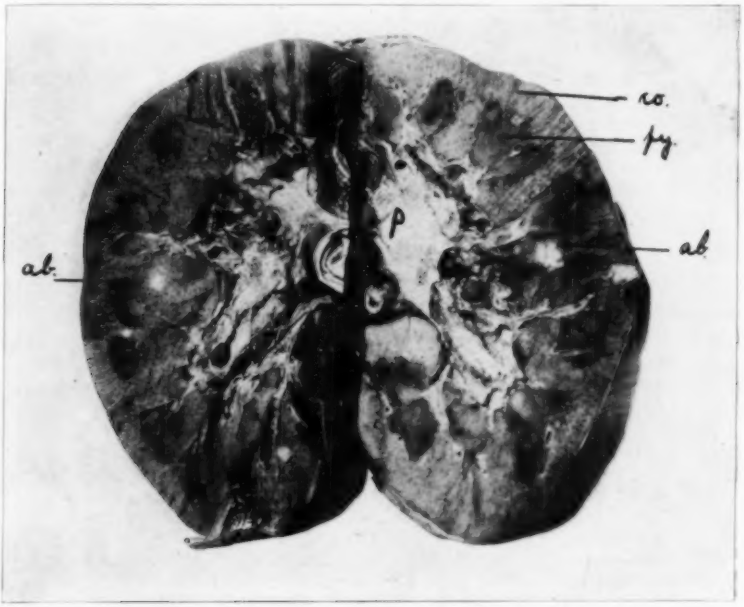

Fig. 2.—Right kidney, Case 22; *co*, cortex; *py*, pyramid; *P*, pelvis; *ab*, blastomycotic abscesses.

On September 14, three days before death, five typical ulcers were present on the face. Fistulas communicating with abscesses existed over the left mastoid, in both forearms, the left thumb, the inner part of the left thigh, in both knees, the tibiae, ankles and dorsal surfaces of the feet. Other abscesses were present over the vertex and the occiput, sternum, clavicle, sixth rib, knee, heel, ankle, inner side of thigh and middle of leg—all on the right side; on the left side other abscesses were present over the heel and external aspect of the leg. Two large confluent fluctuating regions extended from the seventh cervical to the first lumbar vertebrae. Both knees were swollen, fluctuating and tender. General adenopathy was present and emaciation extreme. The other alterations noted previously had changed but little. The patient became delirious a few days before death, which occurred Sept. 17, 1907.

Necropsy.—Permission for a post-mortem examination was obtained two days after death and the following conditions found: Anatomical Diagnosis: Healing and discharging blastomycotic abscesses and ulcers of the skin; blastomycotic abscesses of the bones and muscles; blastomycosis of the lungs, peribronchial lymph-nodes, liver, spleen, pancreas, kidneys, cerebrum and cerebellum; serofibrinous and fibrous pleuritis; parenchymatous nephritis; chronic splenitis; hyperplasia of the mesenteric lymph-nodes; pigmentation of Peyer's patches; fenestration of the Thebesian and aortic valves; patent foramen ovale; decubital ulcers; emaciation.

Fig. 3.—Lower end of femur which was involved in a suppurative arthritis: *ab*, abscess in epiphysis which communicated with the joint; *ca*, eroded articular cartilages.

Both pleural cavities were partially obliterated by fibrous adhesions and contained a considerable amount of slightly turbid fluid posteriorly. The pleural layers enclosing this fluid were covered by a thin deposit of fibrin. Beneath the pleurae of the lungs were a large number of miliary nodules feeling like shot. The left lung weighed 900 gm., did not collapse, crepitated throughout, and small nodules were felt in its substance. The pleura of the lower lobe possessed numerous fibrous and fibrinous tags. On section the lung was brownish-red and on pressure exuded a large amount of frothy red fluid. Many miliary nodules were disseminated throughout the lung. At the apex beneath the pleura (torn

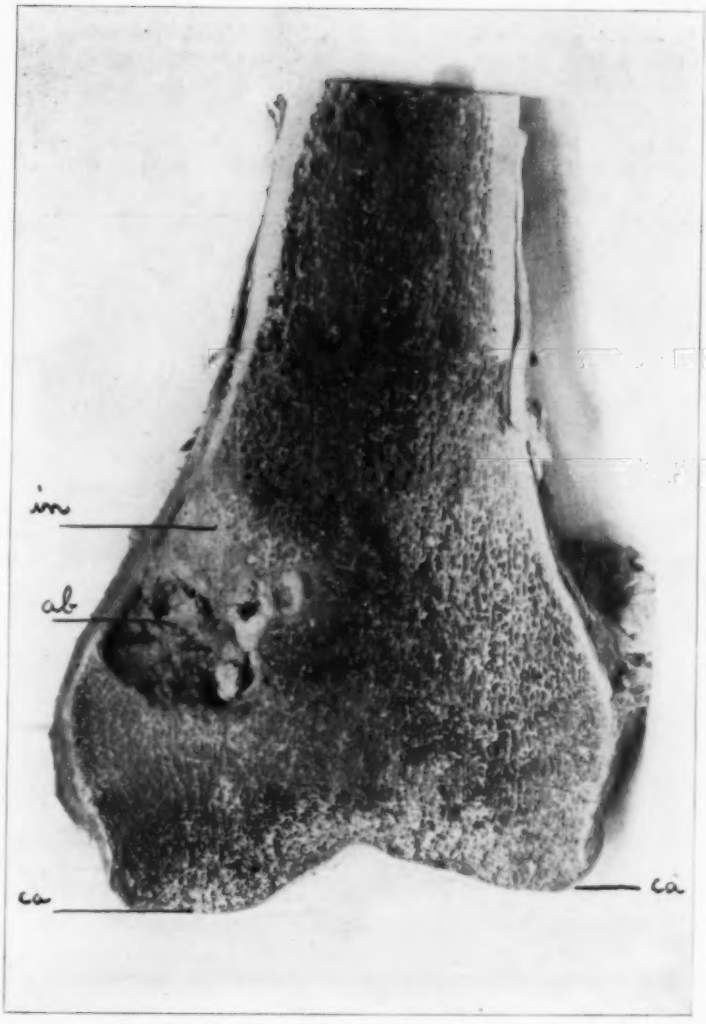

Fig. 4.—Longitudinal section of femur shown in Figure 3: *ab*, abscess in the epiphysis; *in*, infected area, the shape of which suggests infarction; *ca*, eroded articular cartilages.

in removal) were a number of small nodes from 1 to 1.5 cm. in diameter, exuding a purulent fluid on pressure. The right lung weighed 800 gm. The upper lobe was small, firm and covered with a thick fibrous pleura almost cartilaginous in consistence. It contained many solid yellow regions enclosed by radiating bands of fibrous tissue, from which a light yellow purulent material was easily expressed. In the main bronchus of this lung a small opening was found leading into a fistulous passage which extended for a distance of 6 cm. and terminated in a small cavity in the upper lobe. The cavity was irregular, about an inch in diameter and communicated with a small bronchus. Examination of the middle and lower lobes revealed conditions similar to those in the opposite lung (Fig. 1).

The pericardium was normal. In the heart were found a patent foramen ovale and fenestrations of the Thebesian and aortic valves; the other valves were

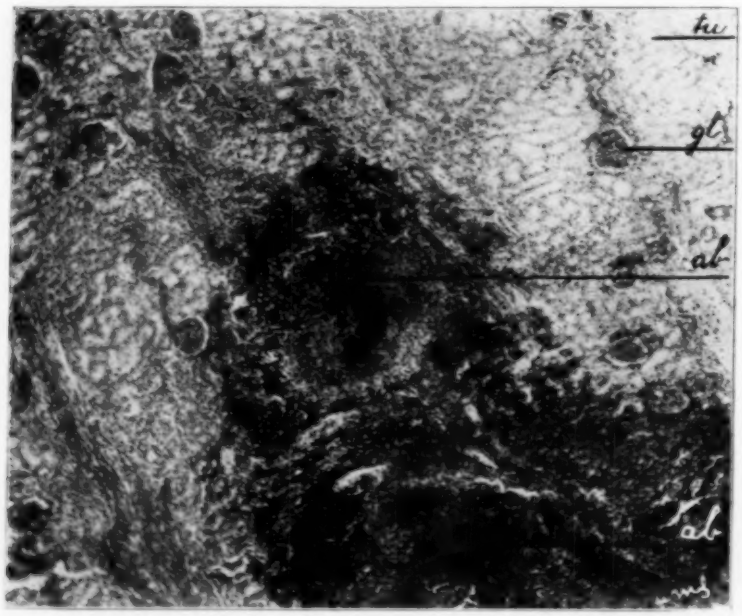

Fig. 5.—Photomicrograph of a blastomycotic abscess of the kidney: *tu*, kidney tubules; *gl*, glomerulus; *ab*, small abscesses which have become confluent.

normal. The myocardium was pale, but no nodules were found in a careful examination.

The pharynx, tonsils, larynx, trachea, and thyroid gland presented no important changes. The anterior portion of the tongue on the left side was somewhat swollen and its surface was roughly granular. The peribronchial and aortic lymph-nodes were enlarged and pigmented and contained a number of yellow nodules.

The peritoneum was smooth and shiny. The mesenteric lymph-nodes were enlarged but contained no nodules. The liver (1,380 gm.) was smooth and dark red. The cut surface was mottled, and after hardening, three very small nodules were found in the interior after considerable search. The spleen weighed 170 gm., was quite firm and had a thickened capsule and trabeculae. Eight small blastomy-

cotic nodules were found in its substance. There was a slight atrophy of the adrenals and pancreas and in the latter a small blastomycotic nodule was found. The gall-bladder and bile-ducts were normal. The stomach was small, its walls were thickened and the mucous membrane dark gray and covered with tenacious mucus. No changes were noted in the intestines, except pigmentation of Peyer's patches.

The kidneys were enlarged and, except for a depressed scar on the surface of the right kidney, the same description applies to both. On section, the cortex was increased in thickness, pale, and rolled out beneath the capsule. The latter stripped readily, leaving a smooth surface and beneath it, as well as on the cut surface, were a number of blastomycotic nodules from 2 to 9 mm. in diameter.

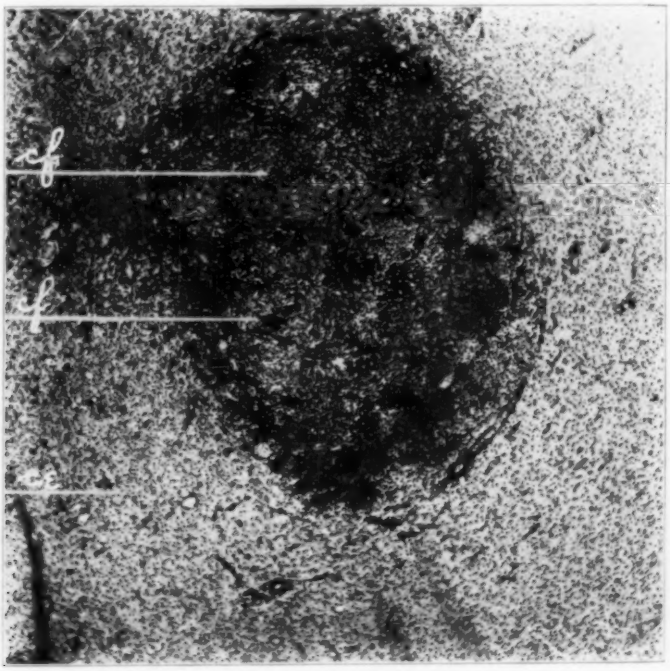

Fig. 6.—A photomicrograph of a blastomycotic abscess in the cerebrum: *cc*, cerebral cortex; *cf*, confluent foci of infection.

A yellow purulent material could be expressed from the largest of these (Fig. 2). The nodules were less numerous in the left kidney. The bladder, prostate gland and testicles appeared normal.

The brain externally presented no changes. After hardening, three small blastomycotic nodules were found in the cerebrum and one in the cerebellum.

The abscesses beneath the scalp were associated with two deep erosions, one in the occipital bone extending to the dura mater, the other in the parietal bone extending to the internal table. The abscess over the sternum communicated with an opening in the manubrium. On section, the greater part of the marrow of the bone appeared to be involved in a suppurative osteomyelitis. On the right side necrosis and softening had taken place and an irregular abscess cavity was

present. The adjacent marrow compartments were filled with yellow pus to the extent that only a small portion of the left half possessed the normal red color. Local abscess formation existed in the first, fifth, sixth and ninth ribs on the right side and in the seventh and eighth ribs on the left side. In nearly all cases the abscess involved the entire shaft, producing a swelling an inch or more in diameter, and in some a diffuse yellow purulent infiltration was found extending some distance from the abscesses. Another large abscess in the pelvis was associated with an area of bone destruction 10 cm. in diameter involving the sacrum and adjacent portion of the right ilium and extending nearly through the bone. The right knee presented a diffuse purulent infiltration of the synovial and periarticular tissues, and some erosion of the head of the tibia was found. Similar conditions were present about the left knee, which contained a still larger amount of pus. The articular cartilages were in some places completely eroded and the surface of the bone hard and smooth (Fig. 3). Two communicating openings

Fig. 7.—Photomicrograph of a blastomycotic abscess of the cerebellum: *ab*, abscess; *gc*, giant-cells; *su*, sulci between the convolutions; *co*, cortex; *gr*, granular layer.

into the end of the femur were found, one on the inner side above the internal condyle, and another posteriorly between the condyles. In longitudinal section an abscess 2 cm. in diameter was found beneath the periosteum, just above the internal condyle. The surrounding cancellous bone was softened for a distance of several millimeters. Beyond this the bone presented a yellowish appearance in marked contrast to the red color of the unaffected bone. The softened area with the abscess was distinctly wedge-shape and suggested infarction (Fig. 4).

Another lesion involving the periosteum and underlying bone was found in the right tibia at about the middle of the shaft. The abscesses about the small bones of both feet and the right wrist were opened and such marked destruction

found that the anatomical structures were recognized with difficulty. Blastomycetes were easily demonstrable in the pus of all the bone lesions.

Histological examination of the nodules found in the various viscera demonstrated the blastomycotic nature of all of them. They possessed so many features in common that it is not essential to describe them in detail (Fig. 5). A rather marked peculiarity was found in the sections of the single nodule of the pancreas, for without the connective-tissue wall surrounding a region of necrosis and numerous organisms, there was no enveloping zone of round cells as is usually found.

The nodules in the cerebrum appeared as though they were caused by the localization of a considerable number of organisms at adjacent points (Fig. 6). The location of the nodules in the cerebellum were chiefly in the granular layer, and an apparent connective-tissue wall was present in and about some of them (Fig. 7).

In the lesions of the bone well-marked walls of granulation tissue were not present about the necrotic areas, and in the adjacent marrow compartments organisms were found unassociated with any tissue reaction.

Bacteriology.—Cultures were made at the necropsy from the blood, pleural fluid and the pus from various abscesses which had not been opened during life. No growth was obtained from the blood or the pleural fluid, but from the pus pure cultures of blastomycetes were obtained. They differed in no respects from those obtained during life from the pus of other abscesses, and a report of their cultural characteristics will be included in a subsequent comparative study.

Thanks are due Dr. E. C. Ryerson, attending surgeon, for permission to report this case.

A CASE OF BLASTOMYCOSIS

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CASE XXIII (5).—*History.*—J. C., man, aged 21, entered Cook County Hospital, Aug. 21, 1907, to the orthopedic service of Dr. E. W. Ryerson. He was born in Italy, moved to the United States at the age of 1 year, and lived in Chicago since. He went to work at the age of 14, and has been engaged in peddling and factory work. For several months previous to his illness he worked in a tobacco factory and inhaled considerable tobacco dust. He also chewed considerable tobacco while in the factory. When at home he lived under fair hygienic conditions, but during the fall preceding the onset of the disease, after getting into trouble and being expelled from home, he slept in exposed outbuildings and basements. The previous and family history are unimportant.

He caught cold Nov. 15, 1906, and was confined to the house for two weeks, coughing frequently and expectorating bloody sputum at this time. He went to work December 1, and noticed pain in back of neck, and in right side of chest, and was obliged to stop work in a few days because of weakness, especially in the left arm, and was then confined to bed until December 27. At this time he suffered with pain in the back, bloody expectoration and night sweats. After January 1 he improved sufficiently to go to work, but, owing to weakness, was again obliged to return to his home, where he remained for the next five months. He coughed, expectorated bloody sputum, suffered pain in back and was quite weak. On May 30 he fell and hurt his back. From that time urination and defecation were involuntary. Two days after the fall he came to the hospital, complaining of pain in side, which was strapped, and he returned home, but the pain persisted for two weeks. On July 1 he was sent to Dunning, where he remained for one month in the tuberculosis hospital; two weeks of this time he was in bed. On August 21, as previously stated, he entered the hospital complaining of painful cough, weakness of the legs and involuntary evacuations. A kyphosis at the level of the second dorsal vertebra was noticed at this time, and in the examining-room the disease was considered tuberculosis of the lungs and spine.

Three weeks after entering the hospital (September 15), he fell while walking about the ward, and was thereafter unable to walk, owing to partial paralysis, and about one month later the paralysis of the legs became complete. Sensation was much diminished in the legs, but was never completely lost. The knee-jerks were increased; ankle-clonus and Babinski's sign also were present. Up to this time the diagnosis of tuberculosis had not been questioned, but the failure to find the tubercle bacilli in the sputum, together with the presence of numerous cutaneous lesions, gave rise to suspicions of blastomycosis. Examination of the unstained sputum and pus from various abscesses was undertaken with the result, at this time quite surprising to us, that the organisms were found quite abundantly present in both.

Examination.—An examination about December 1 revealed the following conditions: The patient lies quietly, seems comfortable, is unable to move the lower, and experiences some pain on motion of the upper extremities. Emaciation is marked and the skin is harsh and dry. He coughs occasionally and expectorates a purulent blood-tinged sputum. The voice is husky and evacuations are involuntary. On the left cheek near the nose is a dull red, slightly indurated, sharply outlined, flat crusted area, 2.5 cm. in diameter, marking the rupture of an abscess, part of which remains as a slightly red fluctuating mass, about 3 cm. in length,

extending downward and outward. On the right cheek, in front of the ear, is a reddish pigmented scar, 2 by 3 cm. at the upper portion of which is a sinus communicating with an abscess the size of a hickory-nut. There is an abscess several times larger at the base of the neck on the left side. The cervical lymph-nodes are enlarged. Several small firm, painless irregularities are present on the ribs, and a tender point on the right fourth rib, in the axillary region. The lungs are hyperresonant with the exception of the right apex anteriorly and the upper lobes and upper portions of the lower lobes posteriorly, over which resonance is impaired and dry râles, bronchial breathing and bronchophony are heard. Over the remainder of the lung the respiratory sounds are roughened and prolonged. The area of heart dulness is normal, the tones clear and regular.

The abdomen is distended and tympanitic and contains no masses or tender regions. The liver extends to two fingers below the costal margin. The spleen is easily palpable, and on deep inspiration extends three fingers' breadth below the costal arch. At the point of the kyphosis previously mentioned a large flat abscess is present which is 10 cm. in diameter, and on the posterior surface of the right shoulder is another, soft and fluctuating and 7 cm. in diameter. A third is present on the left arm and from it small quantities of bloody pus escape. Decubital ulcers are present on both heels and over the sacrum.

An examination of the nervous system demonstrated no changes in reflexes of eyes and upper extremities. The abdominal and cremasteric reflexes are present, although less marked, on the left side. The lower extremities are paralyzed and foot-drop is marked. The patellar reflexes are very weak and the Kernig and Babinski reactions, the Achilles reflex and the ankle-clonus are all now absent. The plantar reflexes are exaggerated and stimulation of the plantar surfaces causes flexion of the thigh and leg, although voluntary motion is absent. Sensation to heat and cold are entirely lost, and to touch and pain much diminished.

Leukocytes and granular casts were often found in the urine, which was usually of low specific gravity. Albumin was absent until the last part of his illness and no blastomycetes were found in the sediment.

An examination of blood, Dec. 5, 1907, showed red cells 4,972,000; hemoglobin 75 per cent. (Talqvist); leukocytes 20,800. In a differential count there were neutrophils 84.3 per cent.; eosinophils 0; basophils 0; small lymphocytes 7.3 per cent.; large lymphocytes 8.3 per cent. Enormous numbers of blastomycetes were regularly found in the sputum, but no tubercle bacilli were demonstrated in repeated examinations. Bouillon inoculated with blood removed from the midvein of the arm, Dec. 3, 1907, remained sterile. Subcutaneous inoculation with tuberculin, Nov. 14, 1907, produced no reaction, but a conjunctival reaction was obtained ten weeks later.

The patient remained in the hospital until his death, which occurred March 14, 1908, a residence of seven months. The course was progressively downward, though some of the symptoms were much abated, and there were periods when the general condition seemed much improved. During November the cough, which at first was very troublesome and painful, ceased to be annoying. The sputum, which in the beginning was profuse and blood-tinged, became much less in amount and the blood disappeared. During January a small amount of voluntary motion returned to the legs. The abscess over the lumbar spine disappeared entirely, but the abscess at the base of the neck became larger and the kyphosis more pronounced, and some crepitus could be obtained over this region. About January 1, pain and tenderness appeared in the left knee and soon afterward both knees and ankles were involved in a suppurative process, which formed discharging sinuses. These joint manifestations were extremely painful, especially during the last month of life.

The temperature was about normal most of the time; often it was subnormal, and occasionally it rose as high as 101 F. for a few hours or a day. The pulse was rather rapid but extremely variable, ranging from 70 to 130 per minute. The

respirations ranged from 22 to 28. During the last two months of life the pulse was constantly above 100, the temperature usually normal or subnormal (occasionally as high as 100) and the respirations averaged about 26.

The patient was given tonics until December 1, calcium iodid, 2 grains, every half hour until January 18, and then potassium iodid from 10 to 30 grains, four times a day.

Necropsy.—(Dr. Stober.)—Permission for a limited necropsy was secured March 15, one day after death, and performed under circumstances which are responsible for the incompleteness of certain portions of the examination. The body had been embalmed and cultural work was not possible.

Anatomical Diagnosis: Multiple blastomycotic lesions of the skin, subcutaneous tissues, muscles and bones; blastomycosis of the lungs, peribronchial lymph-nodes, and spleen, passive congestion and edema of the lungs, parenchymatous degeneration of the kidneys and liver; bilateral fibrous pleuritis; decubital ulcers; anasarca; kyphosis; general emaciation.

The upper part of the body showed extreme emaciation in contrast to the abdomen and lower extremities, which were markedly edematous. Decubital ulcers the size of the palm were present over both hips. On the left side of the face was a circular scar with margins still red and slightly crusted. A small fluctuating area could be felt in the deep tissues beneath. Another marking the site of an old abscess was present in front of the right ear. Behind the right shoulder was found a large fluctuating abscess which seemed to be confined to the subcutaneous tissues; a much larger one was found over the upper part of the spine extending to either side for a distance of several inches. A kyphosis of the spine involving the last cervical and the first two dorsal vertebrae was present at this point. The spines of the vertebrae were separated from each other more than usual, and manipulation of the spine of the first dorsal, which was the most prominent, elicited a distinct crepitus The kyphosis could be reduced and exaggerated to a considerable extent by extension and flexion of the neck on the chest. An external incision was here not allowed.

An examination of the fistulas connecting with underlying abscesses over both knees and ankle-joints demonstrated eroded bone at their bases, but further examination of the bones was not allowed. On opening the chest, the pleural cavities were found practically obliterated by fibrous adhesions. These were very firm at the apices, especially on the right side, where dense cicatrical masses were present. The lung was torn at this point on removal and presented a fistulous opening which communicated with a cavity in the upper lobe, and extended posteriorly between the first and second ribs, the adjacent margins of which were sharp and eroded. No direct communication with the abscess in the back could be demonstrated by pressure on the latter.

The bodies of the vertebrae from the front appeared normal. The anterior surface of the second thoracic was covered with the fibrous tissue involving the right pleura. This vertebra was removed with the bone forceps, and a small portion of the spinal cord was exposed but appeared normal. The cancellous tissue of the bone was normal. Further examination of the vertebrae and back was not allowed.

The lungs together weighed 1,100 gm. Both showed thickened pleurae with numerous fibrous tags. The upper lobe of the right lung was torn in removal as described. This lobe was small and quite solid, although slight crepitation could be obtained in the lower portion. In the upper portion of the lower lobe and in the middle lobe could be felt a number of nodules. On section, the greater part of the posterior portion of the upper lobe was occupied by an irregular cavity which communicated with one of the bronchi. The main bronchus was dilated to form another small cavity at about an inch from the bifurcation. The surrounding tissue was fibrous in character and contained a number of yellow necrotic regions measuring from 3 to 6 mm. in diameter. Between these and also in the anterior portion of this lobe, the middle lobe and the upper half of the

lower lobe, were numerous miliary nodules, some of the larger of which were necrotic. Coal pigment was present to a considerable extent, especially in the affected parts of the lung. Considerable frothy fluid could be expressed from the lower lobes (Fig. 1). The left lung crepitated freely throughout, except at the apex where a large radiating scar was present, extending into the lung for a distance of several centimeters. On section, the lung was dark red, and bloody frothy fluid could be expressed. Small nodular fibroid masses throughout the

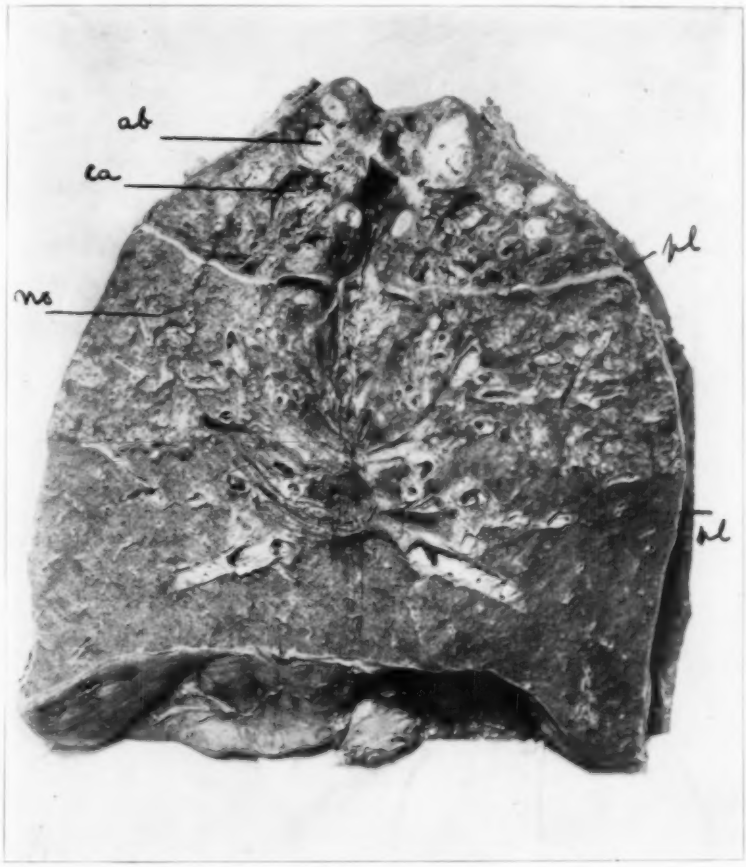

Fig. 1.—Right lung, Case 23: *ca*, bronchiectatic cavity in the fibroid upper lobe; *ab*, abscesses whose contents were inspissated and surrounded by a wall of connective tissue; *no*, blastomycotic nodules in the lower lobe, which from their distribution seem to be bronchogenic in origin; *pl*, thickened pleura.

lung were cut through. The bronchi were here as well as in the opposite lung thickened and prominent. The peribronchial lymph-nodes were enlarged, from 1 to 3 cm. in diameter, and dark red to black on section. Two of them contained several small encapsulated necrotic regions and also a few miliary nodules.

The heart, empty, weighed 255 gm. The pericardium on the anterior surface presented an area of fibroid thickening 3 cm. in diameter. The valves appeared normal. The musculature was a light brown, and in numerous sections no nodules were found. Nothing of importance was found in the thyroid, esophagus, stomach, intestines, pancreas, bladder, prostate or adrenals. The liver was much enlarged and its anterior margin was considerably rounded. The cut surface was light yellow and fat droplets could be seen in the material scraped from the surface. On section of a portion of the right lobe, one small nodule 2 mm. in diameter was found. The spleen was moderately enlarged. The surface was smooth and the capsule somewhat thickened. On section an excess of connective tissue was present, the Malpighian bodies were indistinct and a few miliary nodules were found.

The kidneys together weighed 260 gm. and were normal externally. The cortex was increased, measuring 7 mm. in thickness, and was pale yellow in contrast to the pyramids, which were light red and measured 20 mm. in length. The capsule stripped readily, leaving a smooth surface. No focal lesions were found in either organ.

Histological Examination.—Some difficulty was experienced in demonstrating the organisms in the necrotic material described in the right lung as being surronded by more or less marked masses of fibrous tissue. The lesions in other organs were similar to those described in other cases. Their blastomycotic nature was proved with the exception perhaps of the sections examined of the small nodule in the liver, in which no organisms were found. In other respects this too corresponded to blastomycosis. The sections of the other organs possessed changes indicated in the anatomical diagnosis. No lesions peculiar to blastomycosis were found in sections of the body of the second dorsal vertebra.

Bacteriology.—Blastomycetes were repeatedly demonstrated in the sputum and in the pus from the cutaneous lesions and the various abscesses during life, and pure cultures were obtained from the pus when the abscesses were aspirated or drained. In the mucus removed from the trachea and bronchi at the time of the post-mortem examination the organisms were found.

A CASE OF SYSTEMIC BLASTOMYCOSIS WITH RECOVERY

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LAWRENCE, KAN. CHICAGO

CASE XXIV (6).—*History.*—S. K., a native of Montenegro, aged 39, was admitted to the service of Dr. Slaymaker, April 12, 1908. It was learned through an interpreter that he had been in this country one year, working first as a laborer on a railway for five months, then for two months in Missouri laying pipes. During this time he spent half of each day in a ditch partly filled with water, but declares that he felt perfectly well. The next five months he lived in South Chicago and the last three months he was ill, owing to exposure while looking for work. He lived about two blocks from the lake on the second floor of a frame house built on low ground which was wet and muddy at that time of the year, November, 1907, to March, 1908. Seventeen persons slept in the five rooms on this floor; two or three of them were sick in bed with fever, and although he was unable to give many details of their illness he stated that there was a great deal of coughing. A small cooking-stove in a hall was the only source of heat for the entire second floor of this building.

No history of venereal infection was obtained and the family history was unimportant. This illness began in January, 1908, with intense pain in the chest, cough, fever and weakness. Blood was present in the sputum at first and has continued to appear at intervals since. During the two weeks before his admission to the hospital a number of abscesses developed and the dorsal surfaces of both feet became swollen and tender. He has lost some weight but does not know how much. When he entered the hospital he complained of pain in the feet and ankles. An examination at this time revealed a slightly reddened superficial ulcer about the size of a finger-nail over the left supra-orbital ridge. It was covered with a thick crust under which was bloody pus. Similar lesions were present on the lower right eyelid near the nose and over the angle of the right scapula, and also small pustules on each arm just above the left external malleolus. There were three smooth pigmented scars on the right thigh which the patient ascribed to some running sores connected with the bone, which he had when a boy.

He was well developed and well nourished and obviously not very sick. There was no evidence of consolidation found in the examination of the lung. Slightly impaired resonance was obtained over the right apex and a few crepitant and subcrepitant râles were heard over the region and over both lower lobes. The area of cardiac dulness was increased to the left 2 cm. The inguinal lymph-nodes were moderately enlarged.

About May 1 no râles could be heard in the lungs. Otherwise the pulmonary examination disclosed nothing new. A crusted lesion had appeared on the back of each hand. The pustule on the left leg had developed into an ulcerated crusted lesion 3 cm. in diameter and discharged considerable bloody pus. A subcutaneous abscess 5 cm. in diameter which had developed about the right external malleolus was opened and a large amount of dark bloody necrotic material escaped, and in this blastomycetes were found and pure cultures obtained.

The upper end of the right tibia was very tender, and the overlying skin was red and edematous. The dorsal surfaces of the feet were swollen and tender, walking was decidedly painful and the patient's general condition was somewhat worse. A month later the patient was confined to bed by weakness. The tenderness and redness over the right tibia had disappeared and a small subcutaneous

Fig. 1.—Case 24. This photograph was taken shortly after the vaccine treatment was begun. Three lesions on the face, three on the left forearm and one on the right hand can be distinctly seen.

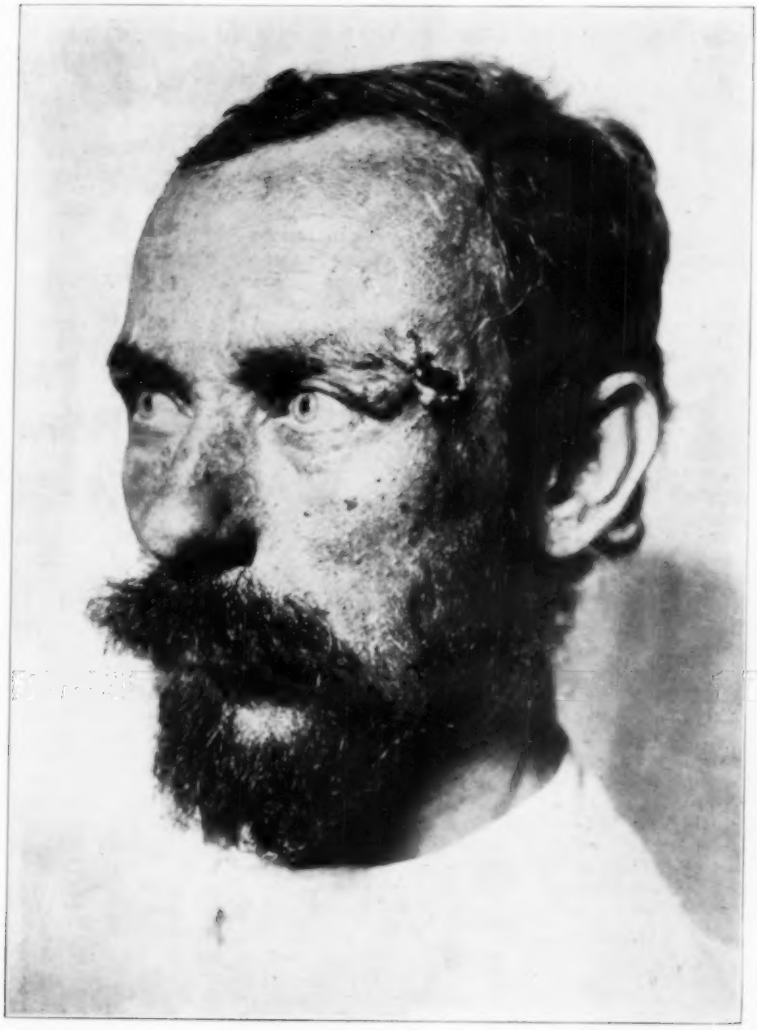


Fig. 2.—Case 24. Taken during the latter part of August, six weeks after beginning of vaccine treatment. The lesions on nose and under right eye have disappeared. The one present near left eye is much improved.

abscess had developed near the attachment of the patellar ligament. The tenderness and swelling on the dorsal surface of the right foot had disappeared completely, and a small subcutaneous abscess had developed on the dorsal surface of the left foot. A small area of redness, tenderness and swelling had appeared over the middle of the left tibia, and a small pustule had developed over the spine of the right scapula. The sputum was still occasionally tinged with blood.

During June two small lesions developed on the nose, one on the right cheek (Fig. 1), six lesions on the left arm (three on the extensor and two on the flexor surface of the forearm, and one on the back of the elbow), one on the back of the left thigh, one on the anterior surface of the right thigh, and one on the outer aspect of the left leg below the knee, making a total of twenty-four distinct superficial lesions, only six of which were present on admission.

It is interesting to note that the arrangement of the lesions was roughly symmetrical. Until July 10 improvement was noted in only two of the lesions in spite of the fact that patient had been under treatment with potassium iodid and copper sulphate from the time of the discovery that the disease was blastomycosis and not rheumatism, for which he had previously been treated. One of these lesions was a small cutaneous abscess at the angle of the scapula which had never been large or deep. This had ceased to discharge and at this time was red and indurated. The other lesion was a swollen tender area on the dorsal surface of the right foot which lasted about three weeks and did not suppurate.

The sputum on repeated examinations showed no tubercle bacilli, but constantly a few blastomycetes. The urine in a number of analyses showed nothing abnormal. An examination of the blood made early in the course, April 30, 1908, demonstrated 5,748,000 red cells and 90 per cent. hemoglobin (Talqvist). The white cells numbered 18,300, of which the polymorphonuclear cells constituted 75 per cent., small mononuclears 17 per cent., large mononuclears 6 per cent. and eosinophils 2 per cent.

Vaccine Treatment.—A vaccine treatment was instituted July 10, and consisted of the subcutaneous injection of the filtrate and suspension of the blastomycetic mycelium obtained from cultures grown in glucose bouillon at room temperature. The temperature up to June 1 ranged from 99 to 100.4 F. and from June 1 to July 10 from 99 to 99.8 F. Seven hours after the first injection (July 10) a maximum temperature of 100.8 F. was noted, returning to normal after two days and remaining so except after the subsequent injection of vaccines, when increases of from 0.4 to 1.4 F. were obtained. With the rise of temperature occurred also a distinct inflammatory reaction about the lesions consisting of pain, redness, swelling and increased discharge, and also a general feeling of malaise. After the second injection, July 15, an active healing of the lesions occurred. The vaccine used in the third injection, July 22, was prepared from cultures of a mold obtained from wood (Fig. 19, p. 537), and the reaction obtained was even more marked and prolonged than from the vaccine prepared from the cultures of blastomycetes. A deep abscess in the right arm suddenly enlarged, approached the surface and ruptured. The site of the injection also became red and indurated and from the swelling a few days later a small quantity of sterile pus was aspirated. The patient by this time was able to walk about in the yard.

Two more injections were given August 10 and August 24, with the result that on September 1 seventeen of the twenty-four lesions previously noted had disappeared. The lesions remaining were still red and indurated but the discharge had ceased and they were much smaller (Fig. 2). The healed or healing condition of the bone lesions was quite apparent in roentgenograms taken at this time and reference to these is made by Dr. Potter, roentgenographer, in a review of the subject (p. 541). On examination of the chest impaired resonance was obtained over the right lung posteriorly with harsh breath-sounds over this area and the upper portion of the left lower lobe. A few dry râles were heard over the right side. The patient's general condition was much improved and

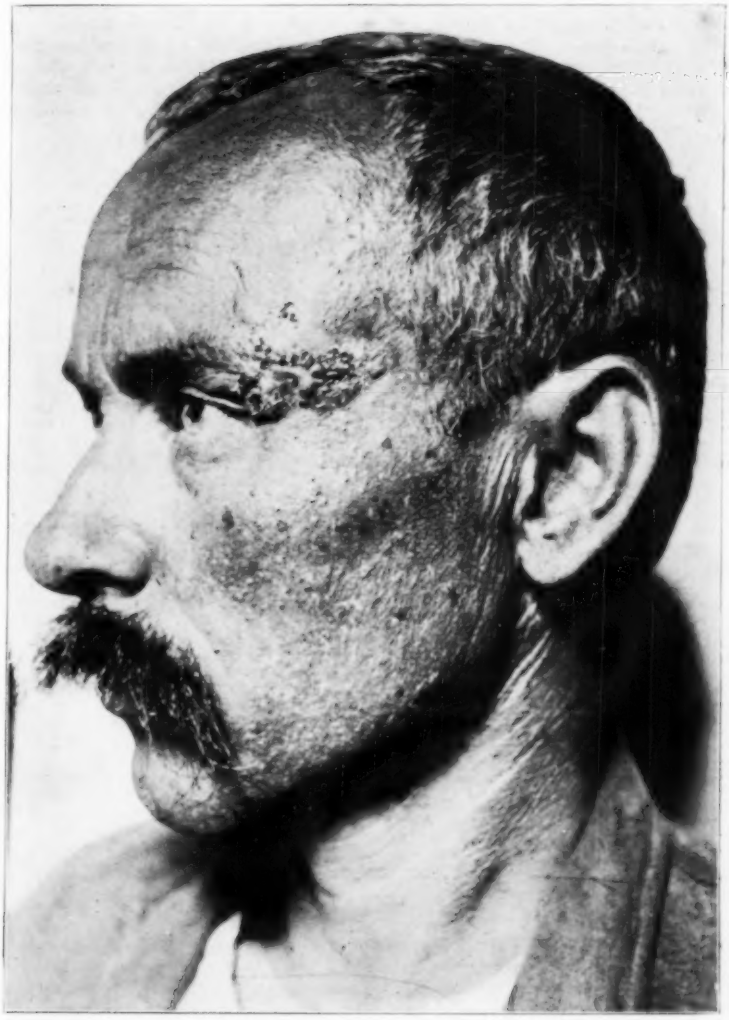


Fig. 3.—Case 24. Taken during latter part of September, showing nearly healed condition of lesion near the left eye.

he gained considerably in weight. Other injections were given September 17, October 13, October 31, November 15 and December 1, when they were discontinued. Of the twenty-seven lesions, all but two seemed to be healed: one on the right forearm, and one on the left side of the forehead (Fig. 3). The patient had gained much in weight and felt better.

The results of the blood examination made September 17 were as follows: white cells 11,000; polymorphonuclears 65.6 per cent.; small mononuclears 21.8 per cent.; large mononuclears 10 per cent.; transitional cells 1.8 per cent.; eosinophils 0.6 per cent., and myelocytes 0.0 per cent. On September 19, 15,300 whites were found, an increase of 4,300 two days after injection of vaccines. Other

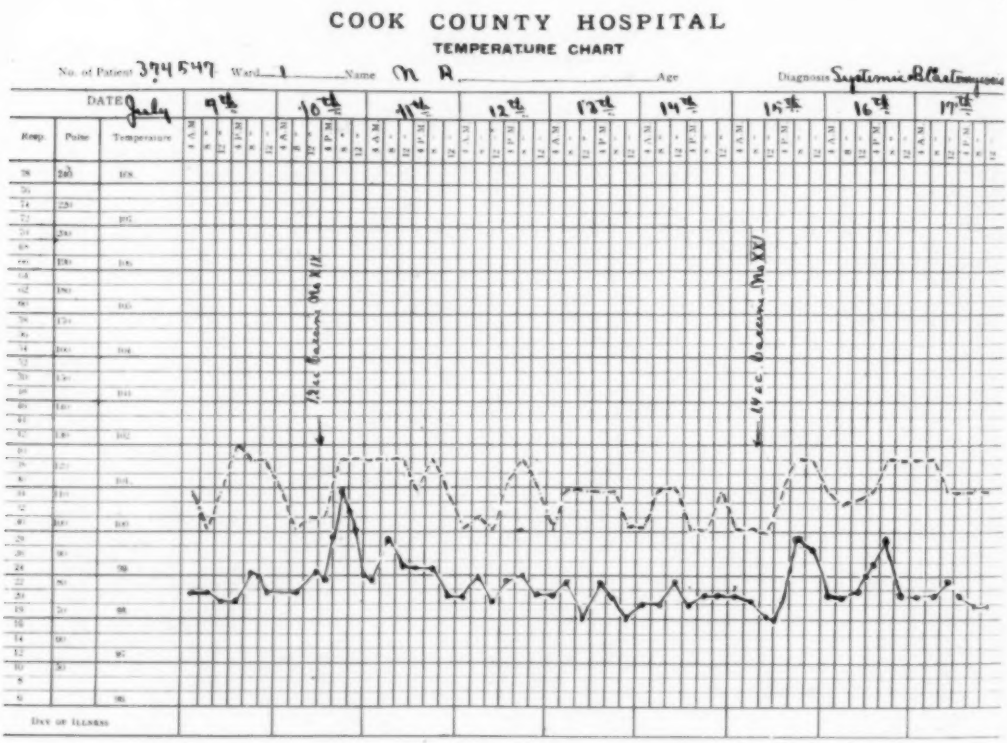


Figure 4.

counts October 13 and October 31 showed little variation from the above except for the increase of large mononuclears to 17 per cent. and the presence in some of these of fine neutrophilic granules, thus approaching the myelocyte in type.

On December 9 the patient furnished the blood for a venous transfusion and was quite weak for a few days but seemed to regain his strength. During January he began to lose weight and the lesion on the right forearm began to discharge. On February 1 a small papillomatous growth appeared on the right ala of the nose and an abscess on the dorsum of the right foot. The latter was opened and drained and the administration of potassium iodid and vaccine (2 c.c. every tenth day) was again resumed, with the result that by April 1 the lesions

on the arm and nose were practically healed, but the abscess on the foot was still discharging slightly. On April 21 he began to complain of a pain in the left chest which increased in severity and was associated with the appearance of physical signs of fluid in the left chest. On May 4 the left chest gave a flat note on percussion below the level of the middle of the scapula; voice-sounds were diminished and breath-sounds absent. At this time the patient was confined to bed and given potassium iodid in doses increased for 20 to 85 grains three times a day and vaccine filtrate from 1 to 3 c.c. every tenth to fourteenth day. A gradual improvement occurred and on June 1 the patient was allowed to walk about in the yard. All evidences of fluid in the chest had disappeared. He left the

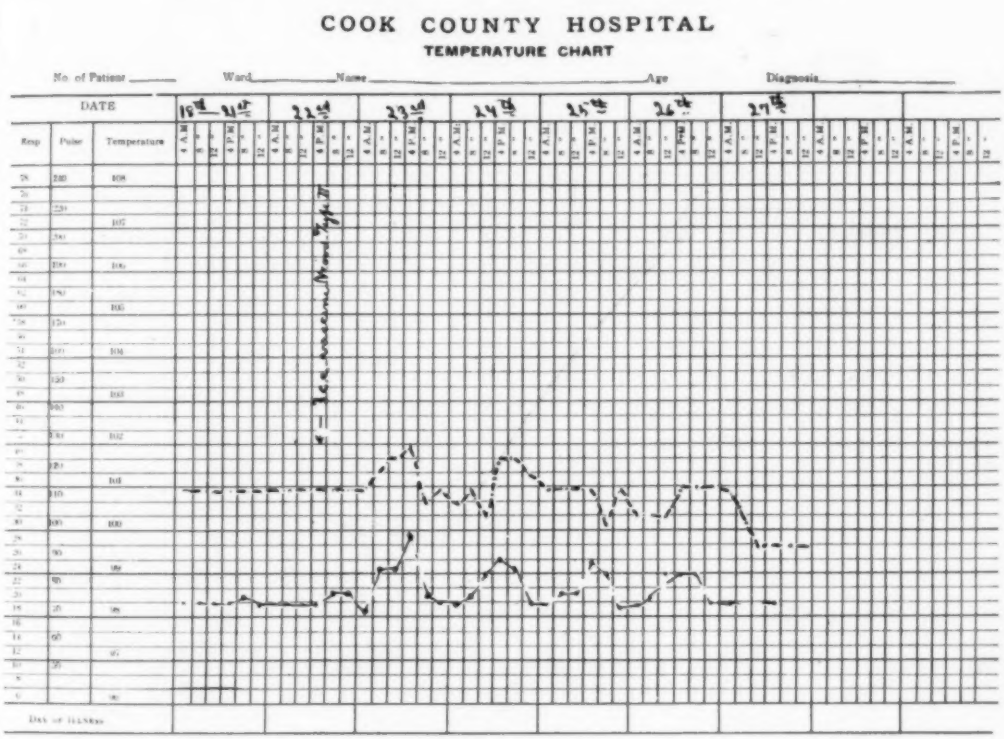


Figure 4.—Continued.

hospital June 19, at which time slight dulness with increased transmission of breath- and voice-sounds were still present over the apices, especially the left, but the cutaneous lesions and the abscess of the foot were apparently healed.

These results indicate that in this case at least the subcutaneous injections of old cultures of blastomycetes were of undoubted benefit. A local reaction in the lesions and a rise of temperature followed each injection (Fig. 4, temperature chart). The intensity of the reaction was also proportionate to the quantity used, taking into consideration,

of course, the immunity which was being acquired. It will also be noted that the culture of the mold from the wood was even more active than the culture obtained from the pus, and that the blastomycetic filtrate was more efficient than the suspension of the triturated growths. Inoculation tests made by applying sterilized bouillon filtrate and mixed cultures triturated in lanolin to the skin which had previously been scarified, gave negative results.

Further inoculation tests were made by Dr. Boughton, with three suspensions of blastomycetes very kindly furnished by Dr. L. Hektoen. Two of these organisms were from Christensen and Hektoen's two cases, and the other organisms isolated by Dr. H. T. Ricketts. A drop of each of the suspensions was placed on the skin of the forearm and the underlying skin scarified. No reaction was observed. Ten days later the test was repeated on the opposite arm using a minute puncture after the manner of Pirquet. In twenty-four hours a distinct papule was present at the site of each inoculation and persisted for four days. The control puncture showed nothing. The ophthalmic test was negative. Inoculation tests by both methods mentioned in several normal cases, and ophthalmic tests in three normal cases gave uniformly negative results.

Thanks are extended to Dr. Slaymaker for permission to report the case.

A CASE OF SYSTEMIC BLASTOMYCOSIS

H. JACKSON, M.D.
CHICAGO

CASE XXV (7).—*History.*—M. M., a native of Croatia, entered the Cook County Hospital May 27, 1908, to the service of Dr. Elliot. He spoke no English and a history was obtained with difficulty. His illness began one year ago with a cough and profuse expectoration which became gradually worse and was associated with considerable loss in weight. Three weeks before entering the hospital a swelling with pain and tenderness appeared in the left arm followed by a swelling of the forearm and hand. A week later ulcers developed in the skin of the face and other parts of the body and progressed quite rapidly.

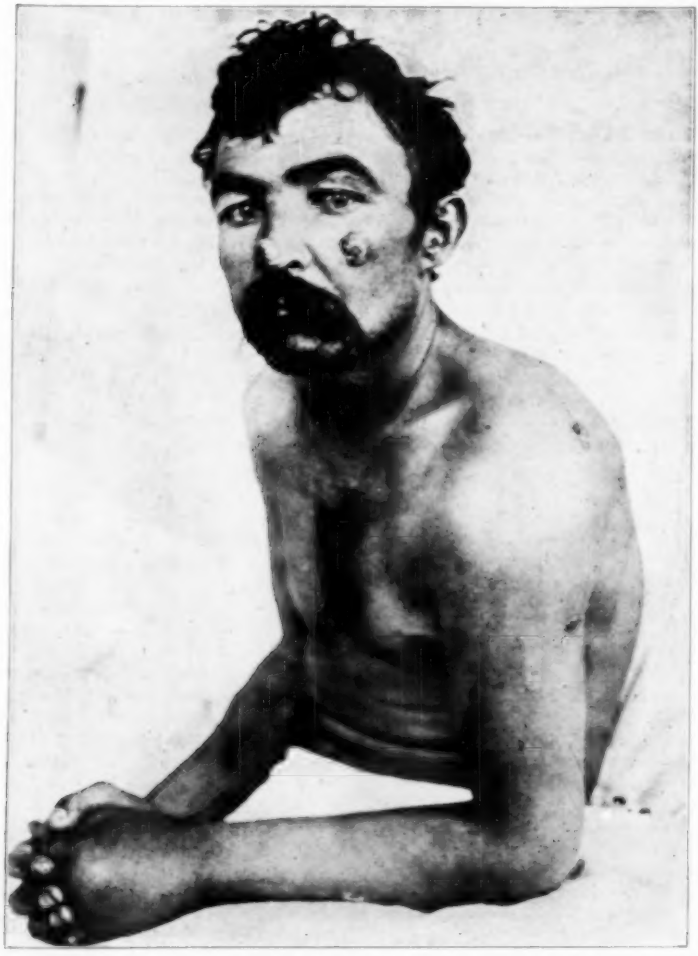
The family history was unimportant. The patient had experienced no serious illness and no venereal infection. He had been a farmer but after coming to this country a year ago he worked as a laborer on a railway. For the previous three months he was unemployed and lived in South Chicago. He drank considerable beer and whisky and smoked many cigarettes each day.

On examination the patient stated that he felt well and desired to return to his native land. He appeared somewhat emaciated and coughed frequently, expectorating bloody purulent sputum. The respirations ranged from twenty-four to thirty, the pulse from 90 to 100 per minute, and the temperature from 98.6 to 101 F. At this time there was on the nose an oval papillomatous lesion from 2.5 to 3.5 cm. in diameter with a raised margin and a base covered with a blood-stained crust under which was a quantity of brown pus. A similar lesion 2 by 3 cm. in diameter was present on the left cheek. Other smaller lesions were present on the left arm within the area of induration previously described, over the left scapula, the coccyx and on the scrotum. A larger one 3 by 4 cm. in diameter was found on the left buttock.

No changes were found in the scalp, eyes, ears or throat. Anteriorly in the neck small, hard lymph-nodes were palpable. The indurated upper half of the left arm was extremely tender, and fluctuation was obtained in its inner border. The forearm and dorsum of the hand were edematous and the arm could not be moved without considerable pain. (See accompanying illustration.) The joints and other extremities were not affected. The respirations were frequent, the supraclavicular and infraclavicular spaces deepened and the apex-beat of the heart not visible. Percussion elicited impaired resonance over the upper lobes on both sides, where tactile fremitus was increased. Over the right side of the chest posteriorly bronchial breathing and prolonged and high-pitched expiratory sounds were heard. On the left side over the upper lobe there were harsh breath-sounds but no râles.

The area of cardiac dulness was not increased, and the sounds were normal. The arteries were sclerotic, the pulse full, strong and regular. The abdomen was distended and tympanitic; the liver and spleen not palpable. At the middle of the external surface of the left testicle was a hard nodule 1 cm. in diameter. The epididymis also contained a hard nodule the size of a split pea. The right testicle and prostate were normal. No changes were found in the nervous system. Examination of the blood revealed 65 per cent. hemoglobin (von Fleischl) and 13,000 leukocytes; the polymorphonuclears numbered 90.4 per cent., small lymphocytes 4.8 per cent., large lymphocytes 2 per cent., eosinophils 2 per cent. and basophils 0.7 per cent.

Bouillon inoculated with blood from the median vein remained sterile. The urine was clear, amber in color; specific gravity 1.015; reaction acid; no albumin or casts present.



Case 25.—Cutaneous lesions on the nose, left cheek and shoulder, also a swollen condition of the left hand secondary to an abscess in the arm.

Many blastomycetes were demonstrable in the sputum, but tubercle bacilli were absent. Round and budding blastomycetes were found in the pus from the cutaneous lesions and the abscesses, and afterward cultures were obtained.[1]

On account of his desire to return to Croatia, he left the hospital unimproved four days after admission.

1. Reference to these is made in another place.

A CASE OF SYSTEMIC BLASTOMYCOSIS WITH NECROPSY

R. E. BECHTEL, M.D., AND E. R. LECOUNT, M.D.
CHICAGO

CASE XXVI (8).—*History.*—On June 28, 1908, a Swede, J. F., aged 38, was admitted to the medical service of Dr. Mix, giving a history of illness beginning in the previous February with a cough, pain in the side and an expectoration occasionally blood-tinged. He had always been a strong robust man of good habits and when taken ill was working in a steam laundry from sixteen to eighteen hours a day. Shortly after the cold began he suffered from pain in the left hip and for this went to a hospital where the thigh was incised and a large amount of pus evacuated. A few days after this operation a papule appeared on the upper lip, suppurated and then became covered over with a crust. Similar lesions developed on the neck, chin, forehead, chest, abdomen and extremities in the order given, and also on the middle finger of the right hand, following, according to his statement, an abrasion. During this period in the hospital, which lasted five weeks, he lost greatly in both weight and strength and the cough and expectoration continued; his illness was considered as tuberculosis.

When admitted to the Cook County Hospital as stated June 28, he was unable to walk, greatly emaciated and dyspneic after much conversing or other slight efforts. The wounds in the thigh, two deep incisions, in which drainage-tubes were still present, were discharging freely and necessitated his lying quietly. The temperature was 101.2 F., respirations 36, pulse 144. Papillomatous ulcers from 2 to 4 cm. in diameter were present on the left side of the forehead, the upper lip on the right side, the back and left side of the neck and the right middle finger. There were many more subcutaneous abscesses which had not ruptured, located as follows: two beneath the scalp, one at the vertex and one over the right ear; two on the back; three on the abdomen; one in the right axilla; three in the left arm and forearm; three in the left thigh; two in the right thigh and one on the back of each leg. These abscesses varied from 2 to 5 cm. in diameter and were for the most part soft and fluctuating. (See illustration.)

Movement of the left thigh was resisted and deep pressure over the crest of the ilium caused considerable pain. The cervical and axillary lymph-nodes were moderately enlarged. Dulness and other signs of consolidation were present over the upper part of both lungs.

Treatment and Course.—The disease was quite promptly recognized as blastomycosis and the organisms found and isolated in pure culture from unbroken subcutaneous abscesses. Roentgen examination of the left hip revealed instead of a joint trouble, a circular defect in the left ilium slightly larger than a silver dollar, and a few weeks later by a similar examination a portion of the crest of the bone was seen lying loose in the abscess cavity. During the two months from the time of admission to patient's death, August 27, the most noteworthy development in the course of the disease was the demonstration of staphylococci and *Streptococcus pyogenes* in some of the unruptured abscesses during a period of slightly more fever and profuse night sweats. An antistreptococcus serum was administered without any marked benefit.

There was some slight improvement during these two months; occasionally the patient was able to spend a portion of his time in a wheel-chair. Some of the abscesses healed after opening and cleansing with iodin. The dyspnea increased toward the end and the physical examination of the chest revealed gradually increasing consolidation until all parts of both lungs were involved.

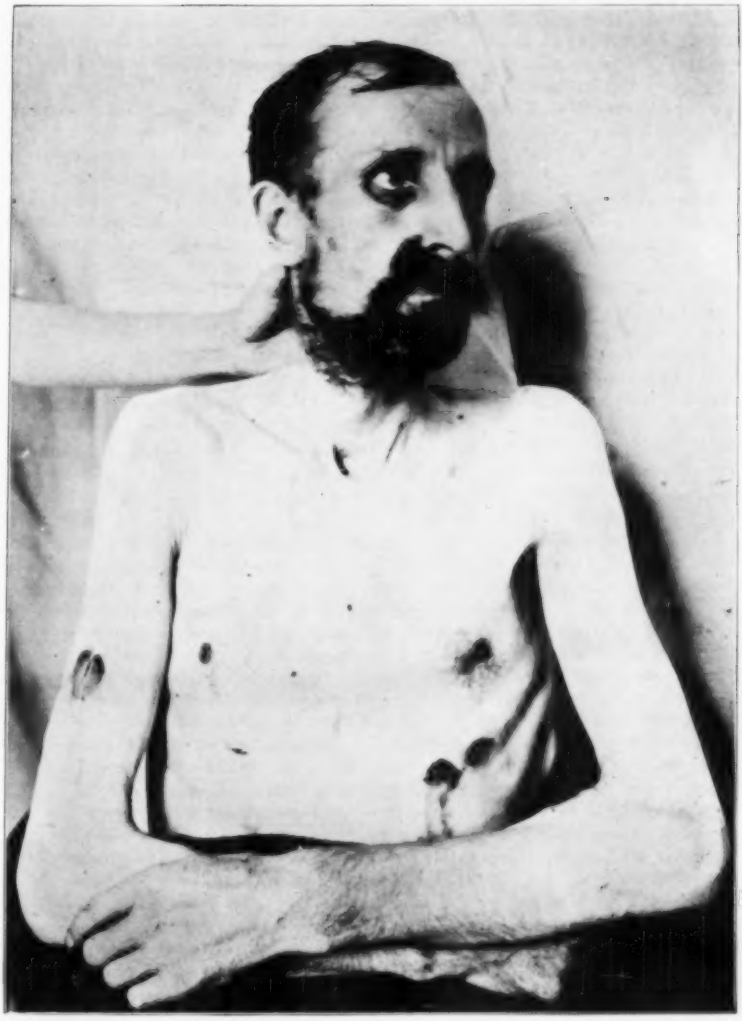
The leukocytes in the blood were never over 9,000 per cubic centimeter. Occasionally small sequestra were discharged from the wound in the left hip, which remained open; over the left ilium crepitus was obtained. In the sputum with the increased pulmonary consolidation the blastomycetes became very abundant; tubercle bacilli were never found. Shortly before death the appetite failed, albumin appeared in the urine and there was some edema of the lower extremities.

The patient was given ½ grain of copper sulphate three times a day and from 30 to 150 grains of potassium iodid. Three injections of a blastomycetic vaccine given in July were followed in each instance by a local reaction and some improvement; two more in August were without benefit.

Necropsy.—The post-mortem examination was held the following day after the body had been embalmed by arterial injection. The anatomic diagnosis was as follows: "ulcerative blastomycosis of the upper lobe of the left lung; disseminated blastomycosis of the lungs, liver, spleen, kidneys, adrenal, brain, subcutaneous tissues and skin; blastomycotic caries of the left iliac and right parietal bones; fibrinous and fibrous pleuritis; hyperplasia of the tracheobronchial, cervical and mesenteric lymph-glands; red marrow in the femur; emaciation; atrophy of the liver; fibrous mural endocarditis; ossification of the thyroid and costal cartilages."

The following are descriptions of the more important lesions: On the face, mostly on the right cheek but extending to the right ala of the nose, is an ulcer with elevated margins with a rather dry floor; 2.5 cm. in its longest diameter, which is downward and to the right into the yellow and rather long moustache. This is the only ulceration on the external surface of the body which has the appearance of any chronicity. The remainder are numerous, and are but little more than recently opened subcutaneous abscesses or the superficial and apparently acute destruction of the skin following such processes. The largest of these is over the left crest of the ilium about 15 cm. from the median line behind. Here is an opening 8 cm. in length with red inverted margins and packed with gauze and containing in its depths loose necrotic bone. The next largest lesion is located midway between the lower angle of the left scapula and vertebrae and consists of a purplish-red oblong necrosis of the skin 6 cm. in its longest diameter, in the middle of which there is an opening into which the terminal phalanx of the middle finger is easily passed into the abscess pocket between two ribs. There are smaller abscesses, the result of a rupture or opening of subcutaneous abscesses on the entire body. There are two on the right side of the face, one on the left side of the forehead, one over the thyroid cartilage, one in front of the left elbow, four on the anterior surface of the trunk, two on the anterior surface of the left thigh, one behind the right knee and one over the middle of the left calf; these are mostly small, from 1 to 2 cm.; gray or yellowish-brown pus can be expressed from them; their openings are small; the skin and subcutaneous tissues are determined. In addition to these are three brownish discolorations on the abdomen on the left side, slightly elevated and fluctuating. Two similar elevated, fluctuating swellings occur, one over the base of Scarpa's triangle on the right side, and another over the internal malleolus (right side). The last two are not discolored externally. These swellings are about the size of hazelnuts. That in the right groin is twice the size of the other; they all contain pus more or less blood-stained.

The changes in the lungs are quite alike. The two pleural sheets are adherent over a region at the apex of each lung equal to the entire palm of the hand in size. Both are fairly firm, probably from the embalming fluid in part, but also from the presence of innumerable closely set gray firm regions the size of miliary tubercles or slightly larger, which are scattered throughout both lungs; more discrete below, more confluent above. In the upper part of the left lung there are a few cavities the size of a hickory-nut. There are enlarged lymph-nodes about both sides of the trachea and in the cervical regions as high as the hyoid bone; there are more on the left side and larger. They vary from a buckshot



Case 26.—Photograph taken July 10, at which time the vaccine treament was instituted. Note the cutaneous lesion above the lip on the right side and the five abscesses in the chest and right forearm. Four had been recently incised, after painting with iodin.

to a hazelnut in size and are firm and red on the cut surface. Such lymph-nodes are also found about the roots of both lungs. The spleen has rounded margins; is 14 cm. long, has an unchanged surface, is firm, and on cutting there is an increased amount of pulp substance seen; it is not very bloody. The Malpighian bodies are distinct and there are a few grayish-yellow spots slightly larger than Malpighian bodies; they are not numerous.

The kidneys are slightly larger than normal and are unaltered except for scattered yellowish lesions mostly in the pyramids, from 1 to 4 mm. in diameter, and the larger ones with softened centers. Four or five such lesions are encountered in single vertical transverse sections. The ureters and bladder are unchanged. The prostate is enlarged. In each lateral lobe abscesses occur containing thick gray pus. On the surfaces exposed by vertical section into each lateral lobe there are a number of irregular cavities, the largest of which would contain a small pea. They are more numerous in the right lobe, in which a spongy or worm eaten appearance to the surfaces is given by the number of abscesses present.

Over the middle of the right parietal bone there is a necrosis of the pericranium 1.5 cm. in diameter. On the inside of the skull opposite this there is a slight yellowish exudate on the dura. The calvarium contains but little diploë. The skull here is thin; there is an extensive necrosis with sequestrum formation of the crest of the left ilium.

In the brain, which was examined very carefully,[1] fourteen small lesions were found in the cerebrum and a few in the basal ganglia and deeper parts of the hemispheres; but most of them were located at the bottom of sulci or at the junction of the gray and white substance. These nodules varied from 2 to 4 mm. in diameter. In the cerebellum there were two larger lesions, one 15 by 11 mm. in the white substance between the dentate nuclei, and above the nuclei, and a second slightly smaller 4 mm. posteriorly.

Histological Examination.—The changes found in sections afforded no essential additional information with the exception of the liver. In this organ minute focal lesions were very numerous. They were about the size of renal glomeruli, located as a rule well within the lobule, and possessed the features common to all the primary minute blastomycotic lesions. So far as could be ascertained the large oblong lesions in the distal portions of the renal pyramids originated from the location there of the fungi in the collecting tubules, and this explanation received some support from the occurrence of small local lesions in the cortex in which both glomeruli and tubules were involved. Characteristic changes occurred in the mediastinal, inguinal and periaortic lymph-nodes, but careful search failed to reveal any in the enlarged mesenteric lymph-nodes. In all the blastomycotic lymph-nodes the alterations varied from minute and widely scattered focal lesions to similar lesion so numerous and coalescent as to occupy practically all of the sections. The chronic changes in the upper lobes of the lungs resembled in the extensive necrotic regions a slowly progressing chronic caseous tuberculosis. In numerous sections there were encountered rounded regions of necrosis which represented occluded bronchi. In the lower lobes the changes were such as have been repeatedly described, the small regions of pneumonia, the replacing of one or more alveoli in some places with single minute blastomycotic focal lesions, in other places a number of such coalescent lesions. In some sections small regions of pneumonia due simply to the filling of the alveoli with leukocytes and fibrin were present; in many sections desquamated cells were abundant in the alveoli; in sections from the lower lobes some emphysema also was found. The regions involved in the adrenals were highly necrotic. In the prostate the sections contained simply abscess walls, and although the surrounding tissues varied, the abscess walls possessed a structure quite like

1. LeCount, E. R.: Jour. Ment. Dis., 1908, xxxvi, 144.

that often met in the subcutaneous abscesses. Nor did sections of the brain lesions reveal anything new; on the whole there was but little tissue reaction, as has been the case with the brain lesions in other bodies previously examined. In some sections of the sternum made from the marrow taken at random and without reference to the presence or absence of contiguous abscesses, numerous lesions in all respects like those seen in other lymphoid tissue were present. They were not coalescent, nor was necrosis marked; similar small focal lesions were present in the spleen; in all places fungi were found in the lesions peculiar to the disease.

A CASE OF SYSTEMIC BLASTOMYCOSIS

F. B. RILEY, M.D., AND E. R. LECOUNT, M.D.
CHICAGO

CASE XXVII (9).—*History.*—S. C., an Italian laborer, aged 31, was admitted to the Cook County Hospital Jan. 11, 1909, to the service of Dr. Ormsby. Through an interpreter it was learned that he had been sick for three months. He suffers from persistent cough which is productive of a purulent, often blood-tinged, mucus. The appetite had been poor and emaciation rapid. Since the onset of his illness numerous cutaneous ulcers and subcutaneous abscesses have developed. He has had profuse night sweats and is now very weak.

Nothing could be learned of his previous illness. During the past year he lived with several other men in a small room under most unhygienic conditions.

Examination.—On examination the anemia and emaciation were quite pronounced. A number of cutaneous lesions were distributed over the body as follows: scalp and left eye, chin, back of neck, shoulder and forearm, right arm and thigh and right side of chest and back. These appeared to be ruptured pustules the site of which was healing and covered with a crust or extending, producing a characteristic papillomatous ulcer. Subcutaneous abscesses from 1 to 7 cm. in diameter existed beneath the skin of the scalp, above the right eye, left cheek and forearm, left thigh and right forearm. The left ankle was swollen and tender, especially over the internal malleolus. Motion was painful and walking difficult. The inguinal lymph-nodes were slightly enlarged. On examination of the chest impaired resonance with diminished transmission of breath- and voice-sounds were present over the apex of the right lung anteriorly and the base posteriorly. Both apices were dull on percussion posteriorly, and increased breath- and voice-sounds were heard. No râles were noted. Nothing of importance was found on further examination. A diagnosis of blastomycosis was made by Dr. Ormsby, who had seen the patient some time before, and this was corroborated by the demonstration of the organisms in the pus and also in the sputum. The pulse was 80, temperature 98.6 F., respirations 24. Although very weak the patient was able to get up and move about the ward. A high evening temperature developed in the next few days, and on January 19 the patient was compelled to remain in bed because of pain in the left ankle. An examination of the blood at this time showed white cells 8,600 per cubic centimeter, red cells 4,464,000, hemoglobin 72 per cent. Two days later the leukocytes numbered 10,800 per cubic millimeter. A differential count showed the following: polymorphonuclears 87 per cent., small mononuclears 2.35 per cent., large mononuclears 7 per cent., eosinophils 1.7 per cent., transitionals 1.1 per cent., myelocytes 0.6 per cent. An examination of the urine also was made but nothing abnormal found.

Treatment and Course.—The patient was given potassium iodid in doses from 15 to 90 grains per day during his stay in the hospital. Larger doses could not be given because of intolerance.

From January 23 to February 25 injections of vaccine prepared from the filtrate of old bouillon cultures of blastomycetes were given in doses varying from 2 to 10 minims. During this time the patient improved considerably; the pain in the ankle gradually subsided, the pulse and temperature became normal and several large abscesses were opened and began to heal. At this time 2 c.c. of the filtrate were given and was followed by a rise in temperature to 101 and an exacerbation of the local lesions. The temperature gradually decreased to 99.6 F., and on March 2 and 3 two more injections of 5 minims each were given followed by slight rise in temperature but no improvement. The injections were discon-

tinued at this time. The temperature a few days later became irregular and high, rising at times to 103; new abscesses appeared and the old ones increased in size. The general condition gradually became worse and the cough increased in severity until April 11, when death occurred. During the last few days of the patient's illness a rigidity of the neck, slight strabismus, exaggerated reflexes, and a positive Babinski sign were noted.

Necropsy.—The post-mortem examination made April 11 concluded with the following anatomical diagnosis: chronic blastomycosis of the upper lobe of the left lung; erosion of the third and fourth thoracic vertebrae; blastomycotic abscess of the root of the right lung; disseminated miliary blastomycosis of the spleen and liver; blastomycotic basilar meningitis; abscesses of the prostate, peritonsillar tissues, epididymis, skin (with ulcers) and subcutaneous tissues; caries of the foot-bones; multiple intercostal, subpleural abscesses; blastomycotic tracheobronchial lymphadenitis. Fibrinous and fibrous pleuritis; fibrous peritonitis; emaciation and anemia; brown atrophy of the heart; atrophy of the liver; slight sclerosis of the aorta and coronaries; emphysema of the lungs; ossification of the thyroid cartilage.

Some parts of the description of these alterations are of considerable value in giving to the reader clear notions of the disease; this pertains especially to the description of the exterior of the body.

"The body is that of a much emaciated man with sunken abdomen. He measures 166 cm. in length. His hair is black and there is a sparse black beard. The ears are small and pinched. There are crusted lesions on the body and face as follows: over the right eye; on the bridge of the nose; the left eye including the lids; over the left zygomatic arch; on the chin in the median line; in front of the right ear and 2.5 cm. outside of the left angle of the mouth. The largest is that involving the left eye; this is the size of a half dollar; the next largest is that between the eyebrows; then in order are the lesions on the chin, the outer angle of the mouth and over the right eye. There are two lesions over the right ear covered by crusts. All lesions when pressed on exude a thick gray pus. A nodule is felt in the neck behind the right sternocleidomastoid the size of a walnut. There are dry crusted lesions at the posterior margin of this muscle, behind on the neck in the median line just below the spinous process of the first cervical vertebra, and two fingers' breadth below this, all the size of a dime. Fluctuation can be made out behind the mastoid process on the left side; the region involved is the size of the terminal phalanx of the thumb; it extends for two fingers below this and a little to the left. There is one small crusted ulcer on the back over the spine of the left scapula, a second one over the middle of the right scapula, and a third lesion opposite the third thoracic vertebra; a fourth occurs over the angle of the tenth rib on the left side. All these lesions are flat, little more than pigmented scaling spots. Many other lesions are present over the rest of the body. Of these eight are on the trunk, seven on the upper extremities and eight on the lower extremities. One of the latter just below the right knee is an abscess which has ruptured. The skin around it is covered by a brown crust; an incision into this demonstrates connection with an eroded bone. The abscess is oblong, 8 cm. long and lying along the outer aspect of the tibia. There is another lesion over the right thigh one hand's breadth below the anterior superior spine. It is 4 cm. across, circular in outline, elevated, fluctuates and the skin over it is not changed.

"The circumference of the trunk at the navel is 59 cm. The right arm may be spanned by the thumb and middle finger, as may also the legs. The right thigh in its middle measures 28 cm."

The alterations in the lungs were in many respects like those repeatedly noted. "The right lung weighs 555 gm. It floats well above the surface; it is mottled externally with brownish irregular spots which are a little sunken and most of which are 3 to 4 mm. in size. Deep in the fissure between the lower and upper lobes is a patch of greenish exudate the size of a finger-nail. The

diaphragmatic surface is cupped and brown in color. The lung is crepitant throughout. The borders are pink and gray, a little rounded and elastic. In the main bronchus there is a mucopus, the lining is smooth and the pus is blood-stained. On section there is exposed near the root an abscess surrounded by dense tissue, the contents of which are the same as the other abscesses, a thick gray-green. The cavity is small and would admit an object the size of a pea. In the lower lobe a grayish region of consolidation is seen; this is elevated above the cut surface. It is 2 cm. long, has a grayish-yellow irregular margin and is located about the middle of the lobe. There are practically no changes in the remainder of the lung. The lung contains bright red blood. The left lung weighs 455 gm. On removal it is torn and the torn surface is twice the size of a dollar. There are adhesions at the apex where this torn region lay along the left side of the upper three thoracic vertebrae. On the whole the left lung externally is similar to the right. It is of a light feathery consistency and there are small, pea-sized flat black, firm elevations of coal deposits on the lower lobe in the fissure. In the region of the apex the lung is somewhat consolidated. On section the cut surface contains a good deal of bright red blood. The bronchi are like those of the right lung as regards their content. The lung under the torn region is dark and beset with minute pin-head-sized regions of softening. The region of consolidation about the torn apex is 10 cm. in diameter.

"There was a small abscess 3 mm. in diameter in the left lobe of the prostate. In the globus major of the left epididymis there was another small abscess."

More interesting than any of these were the changes in the brain and meninges and of these the following record was made: "There are two spots in the dura mater over the anterior portion of the left parietal lobe the size of a penny, and corresponding to them the bone is pink. Over the base of the brain there is a thick gray pus or fibrinopurulent exudate, thickest about the circle of Willis, where the chiasma and corpora mammillaria are completely hidden. This exudate extends out into the beginning of the Sylvian fissure back over the pons and medulla and for a distance equal to the width of two fingers. From these structures it gradually thins out on the inferior surface of the cerebellum. When sectioned horizontally there are exposed in the fundi of the sulci aggregated, and in places single, minute gray regions, some scarcely visible; others, especially on the right side, are so large and numerous as to form a marble-sized lesion. All of these deeper lesions are but extensions of the external process and in none of the sections made are there deeply placed focal lesions which require an embolism of fungi to explain their occurrence. The dura covering the basilar groove of the occipital bone is roughened for an area the size of a split pea; the bone beneath is unchanged." From the cerebrospinal fluid and from two of the subcutaneous abscesses the blastomycetes were recovered in pure culture. In cover-glass preparations of the purulent material used no bacteria were found. The peritoneal fluid and the blood of the heart proved to be sterile.

Histological Examination.—A careful examination of the various viscera failed to reveal any lesions in the internal organs other than those noted in the post-mortem examination. The usual changes were demonstrable in the chronic blastomycosis of the left apex; the peritonsillar and prostatic abscesses, possessed walls similar to the subcutaneous abscesses. The abscess in the peritonsillar tissues in the sections examined apparently had not originated in the lymph-node, for the immediately adjacent tissue was striated muscle; nor did the sections support an origin in the tonsil. In the tracheobronchial lymph-nodes the lesions were small and in all other respects like those found in other cases. In the sections of the dura over the clivus of the occipital bone both fungi and giant-cells were found, but the minute focal lesions were pressed out flat and lay between or on the heavy fibers of the dura much like the similarly compressed "miliary abscesses" seen in the thickened pleura of other cases.

A CASE OF SYSTEMIC BLASTOMYCOSIS

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CASE XXVIII (10).—*History.*—A. F., man, aged 19, entered the hospital April 15, 1909, to the service of Dr. Ormsby. He stated on admission that ten months ago he came from Bohemia where he lived on a farm, and has since worked as a tailor in a sweat-shop on the south side of Chicago. His illness began eight weeks ago at which time he coughed much, expectorating a mucopurulent material which often was tinged with blood. Three weeks later a small painful swelling developed on the back of the right hand. This has since increased in size, and fluctuation has developed. At about the same time a tenderness in the right testicle was experienced. On other parts of the body there developed successively a number of cutaneous and subcutaneous abscesses. The patient has lost about 20 pounds in weight since the onset and is at present very weak and is unable to work.

Examination.—Shortly after admission the temperature was normal, pulse 90, respirations 24. Emaciation was quite marked, and abscesses varying in diameter from ½ to 3 inches were distributed as follows on the forehead, two on the right side of the head and neck; one over the left deltoid region and one in the sixth rib; two on each arm; one in the left calf and one just above the heel on the same side. The left globus major was somewhat enlarged and quite tender. A slight dulness was noted over the right lung posteriorly, being more marked over the upper lobe, where occasional moist râles, harsh breath-sounds and increased vocal fremitus were heard. Prolonged expiratory breath-sounds over the apices were also found. The heart was normal in size and a soft systolic murmur was heard over a limited area at the apex.

The case was at once recognized as systemic blastomycosis and, as expected, many organisms were found in a smear made from pus aspirated from one of the abscesses. The organisms were also subsequently obtained in pure cultures.

In an examination of the sputum, which was bloody, no tubercle bacilli were found, but blastomycetes were abundant. These were also found in the sediment of several centrifuged specimens of urine which otherwise were normal. One week after admission the patient was anesthetized and all of the abscesses were evacuated and swabbed with tincture of iodin. The abscess of the back of the hand was found to be associated with necrosis of the third and fourth metacarpal bones and these lesions are quite evident in a roentgenogram taken at that time. Immediately after the operation the temperature, which previously had been normal, rose to 100.4 F., and this represented the high temperature for the next few days, during which time the patient complained of a pain in the back. April 25 a profuse nasal hemorrhage occurred. In order to determine whether this patient would react to the injection of a blastomycotic vaccine in a manner similar to other cases, 1 c.c. of a filtrate of bouillon culture of blastomycetes was injected subcutaneously, April 27. The temperature on previous days between 4 and 8 p. m. had been 100.4 F., associated with a pulse of 100, respiration 22. On the 28th, one day after the injection, the temperature was 100.6 F. at noon and at 4 p. m. was 102.6 F., pulse 108, respirations 24. On the following day the high temperature was again 100.4 F. and has remained at about this point. Increased pain or changes in local lesions were not noticed.

A differential count of the leukocytes made before the injection showed polymorphonuclears 68 per cent.; large mononuclears 17 per cent.; small mononuclears 13 per cent.; eosinophils 1 per cent. Another examination made May 3

resulted as follows: leukocytes 7,000 per cubic millimeter. Of these the polymorphonuclears constituted 62 per cent.; large mononuclears 13 per cent.; small mononuclears 22 per cent., and eosinophils 3 per cent. The hemoglobin by both Dare and Sahli-Gower instruments was 57 per cent.

Treatment.—Potassium iodid was administered in doses which were gradually increased to the extent that on May 3 the patient was receiving 70 grains three times a day. He was kept in the open air as much as possible and a nutritious diet given. In spite of this the patient seemed to grow weaker and on May 5 six new abscesses about an inch in diameter were found to have developed in the extremities, and the patient complained of pain in the back and left foot. In the latter a small, tender swelling about the second metatarsophalangeal junction was found. Roentgengrams were taken of this region and also of the right hand and the sixth rib, in which lesions existed as described.

On July 12, 1909, it was noted that the patient's general condition was somewhat less favorable. A number of abscesses had healed and new ones had occurred as follows: one over the right scapula; one in the right forearm just above the wrist; one in the left arm, and one under the right eye. The right shoulder was very painful and on close examination the acromial process of the scapula was found to be involved to the extent that displacement was possible. The right thigh also was very painful, but no superficial abscess could be found. The lungs were involved to a greater extent than before, but no other visceral changes were noted. From this time the patient grew gradually weaker and many new abscesses appeared. Death occurred December 13. The necropsy report is as follows:

Necropsy.—The body is that of a young adult white male, 158 cm. in length, considerably emaciated. The hair in the back of the scalp is worn off. On the left side of the forehead near the hair-line is a small triangular scar 2 cm. in diameter. The eyes are sunken. The facial muscles are atrophied. Just below the left orbit is a superficial skin lesion, about 1.5 cm. in length, slightly elevated and crusted. A similar lesion, somewhat hemorrhagic, is present near the right ala of the nose.

Just above the tip of the left shoulder is an ulcerating skin lesion measuring 5 by 3.5 cm. The margins are purplish, contain scar tissue and are slightly elevated; the floor of the ulcer consists of the ligaments of the shoulder-joint, and an area about 1 by 2 cm. seems to connect with the shoulder joint. The anterior aspect of the left shoulder shows a soft, egg-shaped swelling 2 cm. high which fluctuates. On the right arm half way between elbow and shoulder on the lateral aspect is an ulcer measuring about 4 by 5 cm. The margins are scarcely raised, and in the floor exposed muscular tissue may be seen. The right elbow can be extended to an angle of about 120 degrees; crepitus is felt; a soft fluctuating mass is present on the posterior surface just above the olecranon. On the volar surface of the right forearm about 5 cm. below the elbow is an elongated pigmented scar. A few other small scars appear lower down on the forearm. Motion of the wrist is much restricted in all directions, and crepitus can be felt and heard. On the back of the right hand, over the middle metacarpal is an ulcerated area about 1 by 3 cm., communicating with the subcutaneous and interosseous tissue, and on pressure a small amount of mucoid yellowish material can be expressed. About the base of the first metacarpal, a purple fluctuating area may be felt. On the radial aspect of the left forearm about 6 cm. below the elbow is a crusted skin lesion about 2 by 0.5 cm.

Posteriorly just above the spine of the right scapula is a skin lesion about 1.5 cm. in diameter communicating with the deeper tissue, from which a small amount of yellowish mucoid material can be expressed. Just below the level of the twelfth rib at the right of the spine are two small fistulous openings in the skin surrounded by a purple areola, from which a small amount of necrotic material can be expressed. On the right side, about 1 cm. above the level of

the iliac crest is a small ulcerated lesion from which a yellowish cloudy liquid escapes. Over the sacrum is a large decubital ulcer measuring 12 by 4 cm. Both hips are ankylosed in a semiflexed position, and in the left hip crepitus is evident.

A muscular contracture holds both knees in a semiflexed position. About the right knee on the anterior surface are many areas of cicatrical tissue of varying sizes. Just above the left patella is a superficial skin lesion measuring 4 by 2 cm. covered by thin papery scales of epidermis. Near this and to the left of it is a similar lesion about 1 cm. in diameter. On the anterolateral aspect of the left leg about 15 cm. below the knee is a small superficial ulcer. The anterior borders of both tibiae are very sharp and somewhat curved laterally. The left foot, especially on the dorsum, is swollen and puffy. Between the first and second toes of the left foot is a ragged ulcer about 1 cm. in diameter from which grumous material can be expressed.

When the abdominal cavity is opened, the peritoneum is smooth and shining. The omentum is devoid of fat, and is rolled up transversely. The lower border of the liver lies about one finger's breadth above the costal margin in the mammary line. The appendix lies over the brim of the pelvis; it is about 5 cm. in length, is free from adhesions and appears normal. It has a mesentery of its own for its entire length.

The right pleural cavity has posteriorly and laterally a considerable number of easily broken adhesions. The lung is also somewhat adherent to the diaphragm. This cavity contains no fluid. The left pleural cavity is free from adhesions and fluid, except at the level of the fifth rib, where it is firmly adherent to the chest wall. At the site of this adhesion, the fifth rib for a distance of about 2 cm. is considerably eroded, the osseous tissue being practically absent.

When the pericardial cavity is opened, the pericardium is smooth and shining, and contains a small amount of free fluid. The heart is rather small. On the anterior surface of the right ventricle is an area about 1 by 2 cm. which is light in color, slightly elevated, and somewhat thickened. The mitral orifice admits the tips of two fingers. The left ventricle is firmly contracted. The musculature is rather pale. The wall measures 15 mm. The mitral valve is normal in appearance. The foramen ovale is closed. The aortic orifice admits one finger readily. The aortic leaflets are normal in appearance, as is also the base of the aorta. The tricuspid valve appears normal, as do the pulmonary artery and pulmonic valve. The area referred to on the anterior wall of the right ventricle is confined chiefly to the pericardium, but a small whitish area extends into the musculature. The weight of the heart is 200 gm.

The spleen weighs 200 gm. It is somewhat enlarged; the surface is smooth; the consistency is firm. Near the upper pole on the anterior and lateral surface is a slight constriction marking off a small lobule. The surface is purplish; the capsule strips with difficulty. On section, the color is redder than usual; the markings are fairly distinct.

The tongue, trachea and esophagus appear normal.

The right lung weighs 450 gm. The lung collapses somewhat; it crepitates feebly. It shows evidences of fibrous adhesions on all except the anterior surface. The upper lobe feels firm, but no small nodules can be felt. On section the lung is light red; on pressure a small amount of frothy fluid can be expressed. At the base of the upper lobe is an area which is firm, dark purple and airless. On pressure, no fluid escapes from the alveoli, but a small amount of purulent material from the mouths of the smaller bronchi. At the upper edge of this area is a pea-sized cavity containing a small amount of yellow mucoid material. The left lung weighs 400 gm. The surface is free from adhesions except at the base, and at the lower margin of the upper lobe. Very little crepitation is felt. On section, the lung is light in color, and on pressure a very slight amount of frothy fluid may be expressed.

The pancreas is normal in appearance and consistency except that the lobules are rather poorly marked. On section it shows no pathological change.

The liver with the gall-bladder weighs 1,700 gm. The gall-bladder contains a moderate amount of dark bile and no stones. The surface of the liver is smooth; its color is mottled pinkish. On section the color is a rather muddy yellowish-brown, the markings are fairly distinct; on pressure a small amount of bloody fluid is expressed.

The stomach is about normal in size. The rugae are well marked. The mucosa appears normal.

The kidneys together weigh 450 gm. The left kidney is the larger of the two. The surface is pink, and is somewhat irregular. The cut edges do not bulge. The capsule strips readily. The color is pale. The ratio of cortex to medulla is 12 : 18. The markings are indistinct. The right kidney is smaller, but otherwise corresponds to the description of the left.

At the level of the fourth lumbar vertebra on both sides are found abscesses. On the right side the abscess has burrowed laterally about 9 cm. beneath the posterior abdominal wall. Inferiorly, it has burrowed far below Poupart's ligament. On the left side the abscess has burrowed laterally but a short distance. Inferiorly it has burrowed far below Poupart's ligament. Both abscesses have pointed posteriorly. The right side of the body of the fourth lumbar vertebra is somewhat roughened. On chiseling into it, an abscess cavity is encountered which occupies about one-third of the body of the vertebra. It contains a yellow mucoid material. The third and fifth lumbar vertebrae show no gross lesions. The cartilage between the fourth and fifth lumbar vertebrae is quite soft.

The large intestine is negative. The lower portion of the ilium shows a number of small congested areas, but otherwise no change.

Anatomical Diagnosis.—Generalized blastomycosis involving skin and subcutaneous tissue in many regions, left shoulder, right elbow, right wrist, left hip, fourth lumbar vertebra, right lung and left fifth rib; adhesive pleuritis—bilateral; passive congestion of liver; acute splenitis; chronic parenchymatous nephritis; bilateral psoas abscesses (blastomycotic); consolidation at base of right upper lobe with small abscess (blastomycotic).

Blastomycetes were recovered in pure culture from the cavity in the right lung, and were found in smears of the pus from all of the abscesses, but only in the lung were they numerous. The smears were examined for tubercle bacilli, but none were found. The microscopical examination of the tissues will be reported later.

A CASE OF SYSTEMIC BLASTOMYCOSIS

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CASE XXIX (11).—*History.*—J. D., aged 30, Hungarian, has resided in this country for about two years and speaks no English. He was first employed in West Pullman, Ill., for a short time, working in a foundry. He next worked in the car shops, assorting and piling on trucks the various kinds of wood. Patient declares that his hygienic conditions have always been good (good ventilation, no dampness, etc.) and that he has slept alone in a room which he describes as being dry and large enough for two beds. There is no history of any other occupant of the house having had the same trouble as his.

Patient dates his illness from Oct. 1, 1909. Illness started with a bad cold, a severe cough and pain in left side. He does not know if he had fever. Three weeks later he began to cough up blood, at times in large amounts, and he has continued to have bloody expectorations daily, two or three in number, since then. He became dyspneic shortly after the onset of his cough. He does not know how much weight he has lost but says he weighed 160 pounds at one time before his illness started. At present he weighs about 110 or 120 pounds. He has had no night sweats and thinks he has had no fever whatever during his sickness. His appetite has been good. No history of bloody or abnormal number of stools can be obtained. Patient states he has not vomited or suffered any epigastric discomfort. There has been no pain on urination, but he complains of a constant pain in the back which has been so severe as to incapacitate him, and at times keep him from sleeping. Coughing has now ceased for the past two weeks.

About six weeks ago the present lesion over the right eye appeared. A few days later a second similar lesion was noted over the left eye. These were followed in rapid succession by numerous abscesses elsewhere on the face, extremities and trunk, and were accompanied by the usual signs and symptoms of any ordinary localized skin infection. He has been getting weaker all the time and now is unable even to sit up in bed.

The patient entered the Cook County Hospital Dec. 2, 1909, and was admitted to the Tuberculosis Hospital with the diagnosis of pulmonary tuberculosis. It was while there that he developed the skin lesions which aroused the curiosity of the intern, who consulted Dr. O. S. Ormsby as to their nature. The latter made a diagnosis of systemic blastomycosis and patient was transferred to the Skin and Venereal Ward on Dr. Ormsby's service. While he was at the Tuberculosis Hospital, three sputum examinations were made for the presence of the tubercle bacilli but with negative results.

The man's family history throws no light on the etiology. He is married and has two children living and well. Patient drinks several whiskies and about one pint of beer daily. Smokes moderately. Had gonorrhea five years ago. Three years ago he was ill for eight months with a disease of unknown nature. He says that he felt weak, coughed, had no night sweats, and lost little weight. At this time he had no skin lesions of any sort.

Examination.—Physical examination, March 5, 1910, elicited the following: The patient is very much emaciated, highly anemic with a lemon tint to skin; he appears very ill, and is too weak to move about. No cyanosis or dyspnea. No edema of extremities, etc.

Multiple abscesses are scattered diffusely over body. These are of two types: Those of the face and scalp are crusted, globular, about the size of a large hickory-nut, brownish-red and surrounded by a slight inflammatory zone. Some have ruptured, and exude a thick yellowish mucoid material. These lesions are scat-

tered diffusely about the face and scalp. Those of skin of extremities and trunk are not crusted; the overlying skin is but slightly inflamed even in the case of the large abscesses and those of great tension. All are painful on pressure and prevent the patient from moving about. Anteriorly on the chest wall over the seventh rib at its junction to the sternum is a small fluctuating abscess apparently connected with that rib. Likewise an abscess over the region of the sixth dorsal vertebra appears to have communication with the lateral process of that vertebra.

The tongue is badly coated; there is moderate pyorrhea alveolaris; the breath is foul and heavy; tonsils moderately enlarged. A large submaxillary lymph-node about the size of a small hen's egg exists on the left side of the neck; it fluctuates and is tense.

Litten's sign is absent on right side of the chest. There is marked emaciation of chest wall with depression of superclavicular spaces. Motion is restricted in both sides.

Dulness is obtained on the left side posteriorly over lower part of upper lobe and entire lower lobe, and also impaired resonance of right apex, and over entire left lung anteriorly.

Bronchial breathing with fine crepitant râles, increased vocal and tactile fremitus, and exaggerated whispered sounds are noted over the dull area posteriorly on the left side. Mucous clicks are heard over the left lower lobe posteriorly.

Anteriorly a few râles are heard in both axillae, and also fine crepitant râles in both apices. The râles of the dull area on the left side are few in number — the breath-sounds are harsh and roughened with a moderate prolongation of the expiratory murmur. The findings on percussion suggest an advanced pulmonary tuberculosis, while the auscultatory findings would indicate an incipient stage of the disease. No signs of abscess cavity can be elicited. The heart is enlarged a little to the left, and on auscultation an apical systolic murmur can be heard.

The pulse is small in volume and moderate in tension, with a tendency toward dicrotism.

The spleen, liver and kidneys are not palpable.

Except for some adenopathy of the inguinal lymph-nodes, further examination was negative.

The patient's temperature ranged from 98.4 to 103.4 F., with periods of normal temperature for days at a time. No characteristic evening rise or morning subnormal temperature is recorded.

The respiratory rate varied from 20 to 36 according to the temperature.

The pulse-rate ranged from 86 to 110.

Urine: Specific gravity 1.020; acid; cloudy and amber-colored; no albumin; no sugar. Microscopical: Few hyalin casts; few leukocytes; many urates and phosphates; no blood microscopically or chemically.

No blastomycetes were found in the urine on repeated examination.

Blood: Hemoglobin 48 per cent. (Dare and Sahli); erythrocytes 1,600,000; color index 1.46 +; white cells 22,000. Differential count: polymorphonuclear neutrophils 86 per cent., eosinophils 1 per cent., mononuclears, large 9 per cent., small 4 per cent., moderate poikilocytosis.

Blood-cultures were negative.

Sputum was negative for tubercle bacilli and blastomycetes.

Feces: Negative for blood (Weber).

The Wassermann test was kindly made by Dr. J. H. Waugh, and was negative.

A subcutaneous injection of tuberculin (Koch's old), 0.02 mg., was given, increasing 0.04 mg. each dose for three successive doses at intervals of three days. This was done during the period of apyrexia — after the last dose, the temperature was 101 + F. and remained about the same for the following few

days, when it again became normal. Because of the irregular temperature curve, little importance as to the presence or absence of tuberculosis can be attached to the results.

A direct smear from one of the intact abscesses mounted in 20 per cent. potassium hydroxid showed the characteristic morphology of the blastomycetes — budding forms, etc. Cultures from two skin lesions showed the organism in pure culture.

In summarizing it is noted that this case resembles pulmonary tuberculosis in the following: onset with cough, hemoptysis, loss of weight and strength, marked emaciation, lung findings.

In this regard it is noted that the auscultatory findings are insignificant as contrasted with those elicited on percussion, namely, an area of greatly impaired resonance will give few or no râles, etc.

MULTIPLE PRIMARY MALIGNANT TUMORS

WITH A REPORT OF TWO CASES IN DOGS *

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Multiple primary malignant tumors occurring in the same individual are comparatively rare. Götting[1] in over a thousand necropsies on malignant growths encountered only two cases; von Hansemann[2] in the same number of necropsies found five; Redlich[2] in 507 cases had two; Reichmann[2] in 711 cases also had two. Several writers look on these sporadic cases as purely accidental, while others, as Adami,[3] Wooley[4] and Williams,[5] attach considerable importance to them, especially in the further consideration of the nature and etiology of malignant tumors.

In the vast majority of cases, single malignant tumors originate from a single type of tissue, that is (for example), the squamous epithelium, the low cuboidal cells of the mammary acini, or the connective tissue. Malignant tumors are rarely composed primarily of both a transformed epithelium and of a transformed mesoderm. Until 1901, Wells[6] found but three undoubted cases of this type, including his own case, the so-called sarcocarcinomas, all of which had developed from the thyroid gland. In Wells' case the primary tumor was a mixture of a carcinoma with a sarcomatous stroma, giving metastases of pure carcinoma, of pure sarcoma, and of a mixture of both. Herxheimer,[7] in 1908, collected from the literature reports of twenty cases of carcinosarcomatodes occurring in man. There are many cases of this sort of tumor reported in the literature that are not true carcinosarcomatodes, but are mixtures of two entirely

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1. Götting, H.: Zur Multiplizität primärer Carcinome, Ztschr. f. Krebsforsch., 1908-1909, viii, 675.

2. Quoted by Götting. (See Footnote 1.)

3. Adami, J. G.: Concerning the Causation of Cancerous and Other New Growths, Yale Med. Jour., 1901, vii, 309 and 343.

4. Wooley, P. G.: Notes on Multiple Primary Tumors, Boston Med. and Surg. Jour., 1903, cxlviii, 1.

5. Williams, R.: Bilateral Tumors — Malignant and Non-Malignant, Lancet, London, Feb. 1, 1910, p. 426.

6. Wells, H. G.: Multiple Primary Malignant Tumors, Etc., Jour. Path. and Bacteriol, June, 1901, p. 357.

7. Herxeimer, G.: Ueber das Carcinoma Sarcomatodes und einer einschlägigen Fall des Oesophagus, Beitr. z. path. Anat. u. z. allg. Path., 1908, xliv, 150.

separate tumors, namely, a sarcoma and a carcinoma, each having originated separately and later having so thoroughly mixed with one another as to give the appearance of a tumor of single origin. Such a case is reported by Spencer,[8] in which a sarcoma and adenocarcinoma occur close together in the uterus, in places mixed, resembling a true sarcocarcinoma. Closely allied is the case reported by Schöne,[9] in which there is in the thyroid both a sarcoma and a carcinoma, closely approximated, yet quite distinct from each other. Nebesky's[10] case of a spindle-cell sarcoma of the uterus together with a papillary adenocarcinoma adjacent to it exemplifies a similar condition. Some of these cases, then, are indistinctly separated multiple primary malignant tumors.

It is interesting in this connection to point out that Ehrlich and Apolant,[11] by inoculating a typical adenocarcinoma through ten generations of mice, finally obtained a mixed tumor, the stroma of which was a spindle-cell sarcoma. By the thirteenth generation, all traces of the original carcinoma tissue had disappeared, leaving a sarcoma which as late as the twenty-sixth generation was still a typical sarcoma. Sticker[12] reports a similar experience; he inoculated a spindle-cell sarcoma into the mammary gland of a dog. This resulted in the formation of a typical mammary carcinoma. Like results have been reported by Lewin and by Loeb. According to Ewing, in discussing the case of Ehrlich and Apolant, there are four possibilities: first, there is a transformation of epithelial cells into the sarcomatous-appearing cells; second, there is a sarcomatous element in the original tissue; third, the stroma of the original tumor has become malignant, and fourth, the stroma of the host has become malignant.

It is the general conception at present that any one malignant tumor originates from one single primary focus, or in other words, that it is monocentric. Peterson, however, from the study of serial sections of early malignant tumors, believes that a pluricentric origin is the rule rather than the exception. Wooley[4] reports a case of carcinoma of both adrenals in which there are in all five primary foci of similar histological structure. The proximity of these foci, three being in one adrenal, supports Peterson's stand, and makes it plausible that foci still more closely set would at a later stage in the growth of the tumor be conglomerate

8. Spencer, H. R.: Carcinosarcoma Uteri, Tr. Obst. Soc., London, 1905, xlvii, 235.

9. Schöne, G.: Sarkom und Karzinom in einer Schilddrüse beim Hunde, Virchows Arch. f. path. Anat., 1909, xix, 169.

10. Nebesky: Arch. f. Gynäk, 1904, lxxiii, 653.

11. Ehrlich, P., and Apolant, H.: Zur Kenntnis der Sarkomentwicklung bei Cacinom Transplantation, Centralbl. f. allg. Path. u. path. Anat., 1906, xvii, 513.

12. Sticker, A.: Experimentele Erzeugung des Carcinoms beim Hunde, Arch. f. klin. Chir., 1909, xc, 577.

and would obscure its multicentric origin. From the study of very early basal-cell carcinomas, for example, one is impressed by the diffuse area of cells, apparently all primarily on the road to malignancy. In discussing his case of multiple primary carcinomas of the adrenal gland, Wooley states that the adrenal cells surrounding the small primary carcinoma foci appear to be undergoing malignant transformation; he suggests that all the normal cells about these foci are unbalanced and are tending toward malignancy. It is, of course, impossible to determine in tumors beyond their early growth whether or not their initial impetus was from a monocentric or pluricentric origin. One cannot exclude entirely the possibility of a local predisposition, which in a broader interpretation indicates the susceptibility of a certain tissue, that is, the skin, or fascia, or even a system of tissue including, for instance, the mammae, the ovaries, the uterus and the tubes. Thiersch,[13] Adami, Bucher,[14] Warthin,[15] Wooley and others have mentioned local predisposition or susceptibility, in explanation of the occurrence of distinctly separated, though closely seated, primary malignant tumors.

The fact that multiple primary malignant tumors are often bilateral and symmetrical is significant perhaps in many cases of a predisposition on the part of the tissue affected. This predisposition, Williams believes, is a developmental disturbance. A great many instances supporting this view are to be found in the literature. Zangemeister[16] found that out of thirty-nine sarcomas of the ovaries, ten were primarily bilateral. Pick[17] found nine bilateral primary sarcomas out of a series of twenty-three cases of sarcomas of the ovaries. Schubert[18] found three primary bilateral malignant testicular tumors out of a series of fifteen cases of malignant tumors of the testicle. In a series of 114 similar cases, Kober[19] found five bilateral instances. Williams points out that these malignant tumors of the testicle and ovary are more apt to be bilateral when the malignancy has developed early, and in view of this fact connects them with some developmental anomaly. Ladinskie[20] describes a case of sarcoma of one ovary and of a carcinoma of the other ovary in a woman

13. Thiersch: Quoted by Warthin (see Footnote 15).

14. Bucher: Quoted by Warthin (see Footnote 15).

15. Warthin, A. S.: Multiple Primary Carcinoma, Jour. Am. Med. Assn., 1899, xxxii, 963.

16. Zangemeister, D. W.: Ueber Sarkome des Ovariums, Beitr. z. klin. Chir., 1896, xvi, 397.

17. Pick, L.: Zur Symptomatologie und Prognose der Sarkome des Eierstocks, Centralbl. f. Gynäk., 1894, xviii, 940.

18. Schubert: Quoted by Williams, W. R.: Natural History of Cancer, New York, William Wood & Co., 1908.

19. Kober, G. M.: Sarcoma of the Testicle: Conclusions Based on One Hundred and Fourteen Cases, Am. Jour. Med. Sc., 1899, cxvii, 535.

20. Ladinskie, L. J.: Absence of the Uterus and Vagina with Sarcoma of One Ovary and Adenocarcinoma of the Other, Am. Jour Obst., 1898, xxxviii, 78.

in whom both fallopian tubes and the uterus were congenitally absent. In this case anomalous embryonal growth is quite conclusively associated with the development of the bilateral malignancy. Rolleston and Marks,[21] out of twenty-six cases of malignant diseases of the adrenals, found that two cases were primarily bilateral. Walker[22] found ten primary bilateral malignant tumors out of a series of 141 cases of malignant disease of the kidneys. Kuster,[23] in the review of 607 primary malignant tumors of the kidney, found that there were thirteen primarily bilateral. A very remarkable case is cited by Newton,[24] in which ten children out of a family of sixteen died of glioma of the retina before they had attained the age of 5 years. Of these ten cases, seven were bilateral. It is seen from the foregoing instances, which are representative only of a class of cases, that multiple primary malignant tumors may occur in paired organs, and that the percentage of such cases is too high to be considered an incidental occurrence. These cases seem to indicate that a certain type of tissue may be predisposed to malignant transformation under favorable circumstances of irritation. They indicate some anomaly in the embryonal development of that particular set of organs.

Excluding bilateral primary malignant tumors of the ovaries, testicles, kidneys and adrenals, and also the sarcocarcinomas, I have reviewed reports of ninety-five cases of multiple primary malignant tumors; among these ninety-five cases are included the list reviewed by Williams, by Wooley and by Wells. In thirty of the ninety-five cases, there is no predilection for any particular system or type of tissue; twenty-seven of these thirty cases are represented by both a carcinoma and a sarcoma, while the remaining three cases are represented by only one type of malignant tumor. Thirty-four of the ninety-five cases occur in the reproductive system; the mammae, the ovaries, the uterus, the tubes and the vagina are included under this head; only one case in the male is reported. Of these thirty-four cases, sixteen are represented by both a sarcoma and a carcinoma, while in eighteen of the thirty-four cases only one type of malignant tumor is present, that is, either a sarcoma or a carcinoma. Thirteen of the ninety-five cases occur in the cutaneous tissue; two of these are each represented by a sarcoma and a carcinoma, while the remaining eleven are all represented by carcinomas. Again, thirteen of the ninety-five cases occur in the gastro-intestinal tract, including the

21. Rolleston, H. D., and Marks, H. W. J.: Primary Malignant Disease of the Suprarenal Bodies, Am. Jour. Med. Sc., 1898, ii, 383.

22. Walker, G.: Sarcoma of the Kidney in Children, Etc., Ann. Surg., 1898, xxvi, 529.

23. Kuster: Ueber Neubildungen der Niere und ihre Behandlung, Centralbl. f. d. Krankh. d. Harn. u. sex. Org., 1897, viii, 583.

24. Newton, R. E.: Glioma of Retina, Australasian Med. Gaz., 1902, x, 236.

esophagus, the stomach, the intestines, the liver and the pancreas. Of these thirteen cases, four are represented by two types of tumors, namely, a sarcoma and a carcinoma, while the remaining nine cases are represented by but one type of malignant tumor. There are three cases of multiple primary malignant tumors in bones, one case in the central nervous system, and one case in the glands of internal secretion. In all ninety-five cases there are but four instances wherein more than two primary malignant tumors occur in the same individual.

Briefly, then, it is evident that two-thirds of all these cases of multiple primary malignant tumors are confined to systems, while but one-third of the cases are miscellaneously distributed. A comparison may be drawn between the foregoing distribution of multiple malignant tumors and the multiple benign tumors, especially the subcutaneous neurofibromas, lipomas, ecchondromas and fibromas, the occurrence of which undoubtedly indicates some predisposition on the part of the tissue involved. We know that each of these multiple benign tumors is primary, because metastatic distribution can be ruled out. The oft-repeated statement can be reiterated here that "no sharp line of division is possible between the benign tumors and the malignant tumors." This fact, together with the foregoing statistics, indicates and indirectly confirms that multiple primary malignant tumors are, in certain cases at least, due to the existence of some susceptibility on the part of the tissue or system of tissues involved. Adami points out that in the female the involution of all the reproductive tissues at the climacteric is in some way connected with the very frequent occurrence of multiple tumors in this particular system. Williams believes that since the female reproductive system attains physiological maturity earlier than the rest of the body, its chances to develop malignancy are greater.

The type of malignant growth, as seen from the before-mentioned cases, is not so highly important in the consideration of multiple primary malignant tumors as is the system or tissue in which these tumors occur. Many factors, such as irritation, misplaced embryonal rests, climacteric and senile involution, parasites or infection may be involved in the lighting up of these system tumors. But behind these indirect causes which, boiled down, mean "irritation," there is, as far as can be determined, something else which in the interpretation of to-day is called a "biologic" disturbance.

This biologic disturbance may lead to a local, to a tissue, to a system, or to a general predisposition to malignant tumor growth. The recent work of Miss Sleye[25] at the University of Chicago in collaboration with Dr. Wells, has been the most extensive research yet done on experimental

25. Sleye, M.: Statistics to be published later.

heredity of cancer in mice. Their work goes to show that an infective focus of long standing is much more apt to produce a malignant tumor in a cancerous strain of mice than in a non-cancerous strain; in the latter, an infective nodule, or perhaps a benign tumor, instead of a beginning malignant focus, may result from such an irritation. They further point out that multiple primary malignant tumors are much more frequent in these cancerous strains of mice than in the non-cancerous strains. A sarcoma is as apt to crop out in these mice as is a carcinoma. It appears that in the cancer strains there is a definite hereditary predisposition and that this predisposition is general, including all types of tissue and all parts of the body. The best workers in the field of heredity in human cancer have so far failed to find any definite proof of a hereditary predisposition to malignancy.

CASE-REPORTS

The two cases of multiple primary malignant growths reported below occurred in Dogs A and B, both of which were brought to the laboratory for ordinary class-work:

CASE 1.—Dog A, is an old male dog, weighing approximately 60 pounds. In an attempt to insert a tracheal cannula, a large diffusely infiltrating and very vascular growth was encountered in the region of the thyroid (Fig. 1).

Thyroid: The thyroid is firmly embedded in the surrounding soft tissues almost completely encircling the trachea, but not being adherent to or penetrating the latter. In places an irregular thin capsule is present, but it is not defining to the tumor mass. The tumor, which is very irregular, is 13 cm. long and 9 cm. wide, the larger portion lying on the right side. The large veins coursing over and leaving the tumor are almost all filled with papillous, worm-like tumor thrombi, some of which attain a length of 5 cm. The regional lymph-nodes are not involved by metastases, though on the left side two or three are incorporated in the tumor mass.

The cut surface of the tumor is very fibrous with soft centers or nests of cells in it. In places where the stroma is scarce, the tumor is soft and grossly like a small round-cell sarcoma. In either side is a small, necrotic and old hemorrhagic region.

Lungs: The lungs are the seat of numerous whitish-gray nodules, spherical in outline. They range from 1 mm. to 2 cm. in diameter and are about eighty in number.

Mediastinum: In the anterior mediastinum there is a nodule the size of a pigeon-egg, pedunculated and encapsulated. Two-thirds of it is gelatinous; the remainder is solid.

Adrenals: The right adrenal is replaced by a slightly irregular spherical tumor, 5.5 cm. in diameter (Fig. 2). It is surrounded by a thin fibrous capsule in which there are a few small veins. The color through the capsule is distinctly a dirty yellow and brown, quite similar to the ordinary renal hypernephroma. It is distinctly separated from the right kidney by a distance of 1.5 cm. At its inner border there is a nodule, 0.5 cm. in diameter, protruding from it, for a distance of 0.7 cm. The whole tumor is easily enucleated from the surrounding tissue. This adrenal tumor was cut into sagittal sections, 0.7 cm. apart. The section through the center reveals a surface that is for the most part necrotic, although it is rather firm. It is brownish-gray with irregular streaks of yellow through it; at the edges the mottling is of a bright reddish-brown as though

from fresh hemorrhages. At the lower inner pole of the tumor, included within the capsule yet separated from the rest of the mass by a thin fibrous septum, is a crescent-shaped peripheral cap of tissue, 0.7 cm. thick and 4.5 cm. long. This is yellow and solid; it is quite unlike the rest of the cut surface. Other surfaces made by the sagittal sections reveal a similar condition, as just described, except that near the surface of the tumor the necrotic appearance fades and the yellow tissue, mottled with red, is in preponderance.

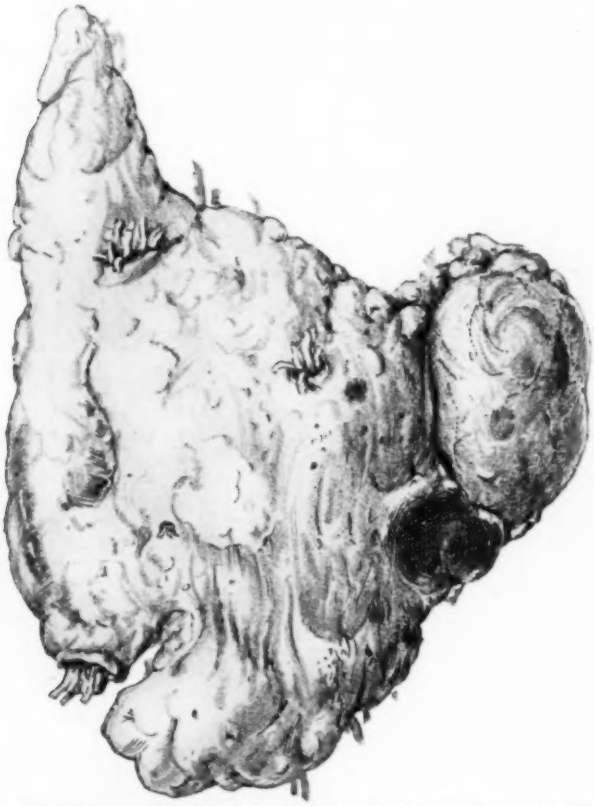

Fig. 1.—(Two-thirds natural size.)—Dog A. Carcinoma of the thyroid. The large veins coursing over and leaving the tumor are numerous and full of papillomatous tumor thrombi. The capsule is thin and ill defining.

The left adrenal is replaced by a spherical tumor 4 cm. in diameter, surrounded by a thin capsule and entirely separated from the kidney (Fig. 2). It is easily enucleated from the surrounding tissue. It is separated from the right adrenal tumor by a space of 4 cm., and no connection between the two is visible grossly. This tumor is a little firmer than the right one. On surfaces made by sectioning, it is seen to be beset throughout by small whirls of yellowish tissue, similar to adrenal cortex in color. These whirls range from 1 mm. to 1.5 cm. in diameter. The largest ones are semineerotic.

Kidneys: Both kidneys are of the congenital multicystic type, the cysts being very numerous throughout both kidneys and ranging from 1 mm. to 3 cm. in diameter (Fig. 2).

Liver: The liver is normal except for a small 1.5 cm. cavernous hemangioma.

General: The rest of the body on careful examination reveals nothing of importance in connection with these tumors.

Microscopic: All the microscopical sections are stained with hematoxylin and eosin.

Dog A: Sections examined from various places in the thyroid reveal an adenocarcinoma, the alveoli of which are well formed in places and contain colloid. The majority of the alveoli are irregular, incomplete and without colloid. In the regions in which alveoli are present, the stroma is thick and fibrous. In the softer and non-fibrous portions of the tumor, the microscopic picture is that

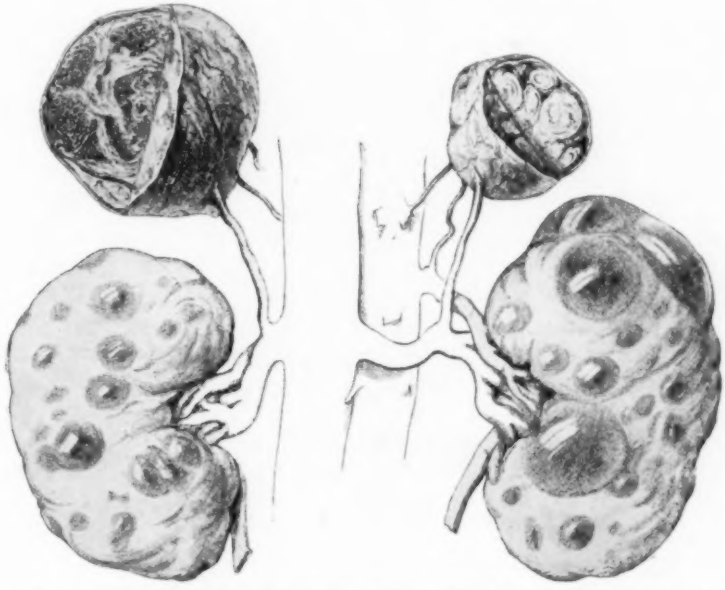

Fig. 2.—(Two-thirds natural size.)—Dog A. Bilateral congenital cystic kidneys associated with bilateral primary adrenal hypernephromas. The right adrenal tumor, with the exception of the subcapsular region, is almost entirely necrotic, with multiple regions of hemorrhage. The left tumor is composed of whorls of tumor tissue, set in a connective-tissue stroma; the large whorls are necrotic.

of a carcinoma simplex; the solid masses here are composed of cells with a small round nucleus, quite granular with chromatin and deep staining with hematoxylin. The cells are very indefinitely outlined, there being a few pink-staining plasma shreds and granules between the nuclei. In these softer regions the stroma is delicate with blood-vessels running through it. Still other regions of the tumor that are most fibrous to the gross examination are composed of almost solid hyalin connective-tissue masses with single cells, chains and irregular groups of carcinoma cells scattered throughout.

Lungs: All the tumor nodules in the lungs are of thyroid tissue, as is the pedunculated nodule in the anterior mediastinum, and also a small nodule accidentally discovered in the region of the pineal body. In the lungs the small nodules are in the blood-vessels; some are necrotic, while others, especially the larger ones, have a fibrous and vascular stroma. Most of the metastases tend to reproduce the same type of carcinoma tissue as was described in the thyroid tumor; some are adenocarcinomatous, while others are more of the carcinoma simplex type.

Adrenals: The microscopic picture is the same for both adrenal tumors, except that more necrosis is present in the sections taken from the tumor on the right side. The capsule is thick and fibrous, yet very irregular in its thickness. In either tumor the picture varies considerably in different places. For

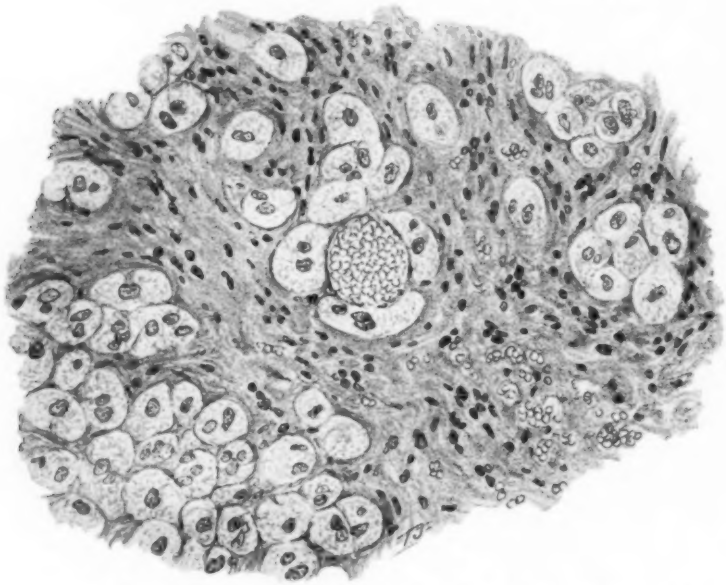

Fig. 3.—Dog A. Central portion of adrenal tumor, represented by a large polygonal cell, having a distinct bladder-like yet often solid nucleus, and a cytoplasm distinctly vacuoled. These cells are arranged in single and in double cordons, in nests, or set singly in a hyaline connective-tissue stroma.

the most part, the central portion of both tumors is represented by a large polygonal cell, having a distinct bladder-like, yet often solid nucleus, and a cytoplasm distinctly outlined and vacuoled (Fig. 3). These cells are quite similar to the ordinary foamy cells in hypernephromas of the kidney. They are arranged in single and double cords, in nests, or set singly in a hyaline-like connective-tissue stroma. Between the columns and cords are great numbers of blood-sinuses; in fact, in places the dilated blood-sinuses have crowded and necrosed the tumor-cells.

In other places, smaller cells with a deeper-staining nucleus and a less defined cytoplasm are found in large masses. Between the cells a very delicate, embryonal connective-tissue stroma is found. This type of formation is mixed rather thoroughly in places with regions of the above-described foamy cells.

Just under the capsule in places is found an atypical zona fasciculata; these cells sometimes become sarcomatous in appearance, approaching the spindle cell and the large round-cell type.

At the upper inner surface of the tumor on the right side, the cells under the capsule can be recognized as atypical cells of the zona glomerulosa. Their cordons are very irregular, being composed of flattened indistinctly outlined cells with deep staining irregular nuclei; they are continuous with large thick solid bundles of oval cells, the outer layer alone being recognized as cells from the glomerular zone.

In the moon-shaped cap described in the gross, lying on the lower border of the right adrenal tumor, there are masses of medullary or chromaffin cells, sharply angular with a large amount of eosin-staining cytoplasm. They are somewhat larger and more irregular than the normal medullary cells, and in mass are separated sharply from the surrounding tumor tissue.

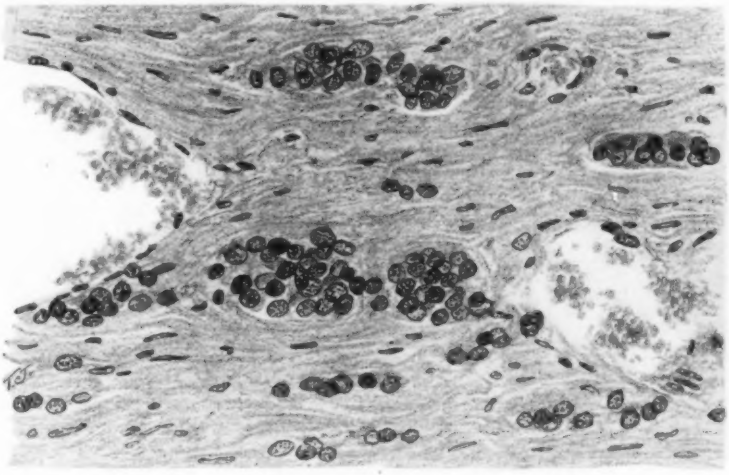

Fig. 4.—Dog A. Capsule of adrenal tumor infiltrated by strings and small masses of tumor-cells. The cells are polygonal, with a small amount of dense purplish-staining cytoplasm, and an irregular deep-staining nucleus.

The capsule of both the right and the left tumor is infiltrated by strings and small masses of tumor-cells arranged quite like the strings of carcinoma cells at the edge of a carcinoma simplex (Fig. 4). These cells are medium-sized polygonal cells, with a purplish-staining dense cytoplasm and an irregular deep-staining nucleus. For the most part, these chains of cells do not penetrate except into the inner two-thirds of the capsule. In several places, however, they have broken through the capsule (Fig. 5) and are found in irregular masses in the loose connective tissues on the outside. Small bunches of them are found in large spaces, apparently lymph-spaces in the connective tissue and areolar tissue outside the tumor. Their appearance outside of the capsule is a little different from that within the interstices of the capsule, in that, outside, both the nucleus and the cytoplasmic outline of the cells are irregularly flattened. The capsule is entirely broken through in places by masses of these cells. In several sections are found irregular giant-cells of the myeloid type, either singly or in small groups. In no place throughout either tumor are there any tubule formations

like those described in about half the cases of renal hypernephromas. Histologically, both tumors are essentially solid.

There are veins on the surface of the right adrenal capsule that have been thrombosed, the lumen now being in the process of canalization. A careful search for adrenal metastases was made in other parts of the body, but none were found.

As a summary of the anatomical findings in Dog A, there are: (1) adenocarcinoma of the thyroid with metastases in the lungs, mediastinum and pineal region; (2) bilateral primary adrenal mesothelioma, the local picture being that of early though definite malignancy; (3) bilateral congenital multicystic kidneys; and (4) cavernous hemangioma of the liver.

CASE 2.—Dog B is a large, old female. The neck is diffusely enlarged, while in the posterior mammary region there is a nodular, rather soft mass from 4 to 6 cm. in thickness, 8 cm. wide and about 13 cm. in length.

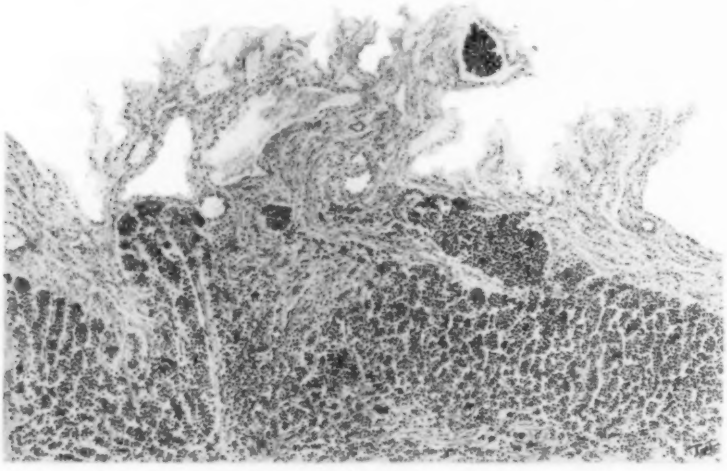

Fig. 5.—Dog A. Capsule of adrenal tumor under low power. In several places the tumor-cells have broken entirely through the capsule and are found in irregular masses in the loose connective tissue outside, and also in large spaces, apparently lymph-spaces.

Thyroid: The thyroid gland is quite like that of Dog A with the exception that it is not quite so fibrous and not so large. There are a few lymph-nodes in the cervical region of both sides that contain white metastatic tumor-nodules. The tumor is very vascular, the vessels containing numerous papilliferous tumor thrombi.

Lungs: The lungs alone contain thyroid metastases, of which there are about fifty, ranging in size from 1 mm. to 1 cm. in diameter. They are spherical and of a whitish-gray color.

Mammary Tumor: The right posterior mamma is more involved than the left, though both are involved by the tumor. The skin is immovable over the mass but is not ulcerated. The tumor is roughly nodular, the nodules being from 2 to 5 cm. in diameter, and indistinctly separated from one another by a softer internodular tissue. On the surface made by sectioning the tumor it is seen that the border of the tumor is indefinite in its separation from the surrounding normal tissue; in places it has a very delicate capsule. The region

between the nodules is milky white, and soft or gelatinous in consistency. These nodules are nothing more than irregular firm cartilaginous centers surrounded by softer tissue. The transition between the soft and the firmer tissues is a very gradual one.

Adrenals: The adrenals are twice as large as normal. They are firm in consistency.

The remaining tissues reveal no pathological changes that are of importance in this case.

Microscopic: The tumor of the thyroid is of the adenocarcinomatous variety, tending toward the solidum or simplex type; in this respect it differs from the carcinoma of the thyroid in Dog A. The alveoli here are incompletely formed in most instances, and contain a granular eosin-staining substance, more like albumin than like colloid.

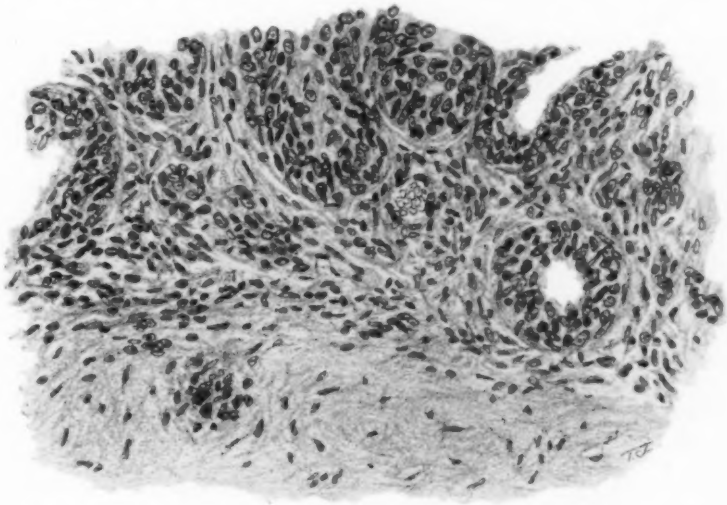

Fig. 6.—Dog B. Mammary tumor. The softer portions of this tumor are composed of a wildly proliferating sarcomatous-like connective tissue, in which there are various-sized tubule formations: some are solid while others have empty lumina, and are lined with cells from three to six layers deep; these cells do not resemble endothelial or epithelial cells, but are of an intermediate type. The above-mentioned type of tissue runs into a myxomatous tissue, and this in turn into an embryonal cartilaginous tissue.

The metastases in the cervical lymph-nodes are similar to the original thyroid carcinoma tissue. The nodules in the lungs are all metastases from the thyroid tumor. They are located in the blood-vessels; the smaller ones consist of irregular cell-nests tending to alveolar formation, in places, set in a hyaline-like tissue; the larger nodules have a distinct fibrous stroma in which there are blood-vessels. The cells, though, in places tending to form alveoli are for the most part arranged in no particular manner.

Mammary Tumor: The edges of this tumor are faintly limited by a delicate connective-tissue capsule which is, in places, lacking. The outermost tumor-tissue, which is a diffusely proliferating sarcomatous-like connective tissue, corresponds to the soft gelatinous internodular tissue described in the gross. The latter has in many places no limiting connective-tissue capsule between it

and the normal tissue. The soft tissue is composed of irregular-sized spindle-cells, the fibrillae of which approach that of embryonal connective tissue in character. The spindle-cells are arranged in no regular fashion, but are confused and run in all directions (Fig 6). Within the tissue mentioned above lie many various-sized, twisted and compressed tubule formations, the lumina of which are distorted and empty. The cells lining these tubules are arranged in irregular stratified formation, from four to six cells deep. They do not resemble endothelial cells or epithelial cells, but are of an intermediate type.

In the centers of the tumor nodules there is invariably found a cartilaginous tissue which is not mature or typical in any place. At its edges it fades into a myxomatous tissue, into a mucoid substance, or into the above-described sarcomatous-like connective tissue. This microscopic picture is quite identical with that of the mixed tumors of the parotid gland described by Wilson and Willis.[28]

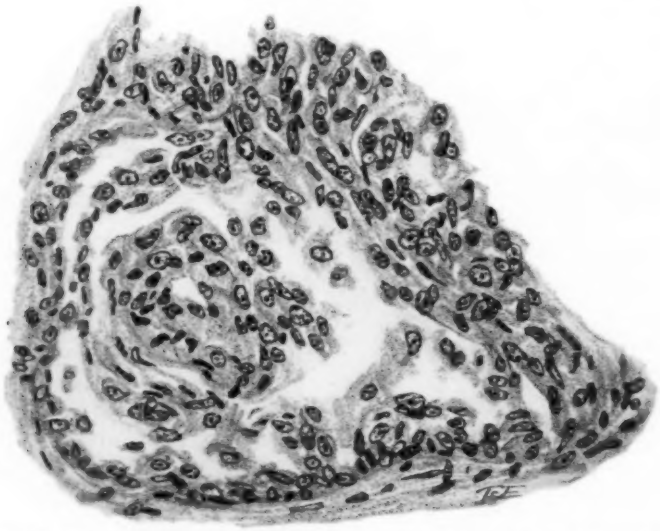

Fig. 7.—Dog B. Mammary tumor. A high-power drawing of an incompletely formed tubule, with its surrounding sarcomatous-like connective tissue.

There are no detectable metastases from this tumor, yet the histological character of the sarcomatous connective tissue on the advancing border of the tumor indicates probable malignancy. The older portions in the centers of the nodules are composed of a tissue approaching the adult type. The peripheral portions can be considered as a more embryonal and undifferentiated mesodermal tissue.

Adrenals: These, though grossly normal except for slight enlargement, are very interesting histologically, in that from fifteen to twenty-one small intracapsular adenomas, composed of cells similar to the zona glomerulosa, are found in any one cross-section.

Briefly, then, in Dog B there are the following: (1) adenocarcinoma of the thyroid gland with metastases in the lung; (2) mixed tumor of the mammary gland (chondrosarco-endothelioma); and (3) multiple adenomas of the adrenal capsule.

28. Wilson, L. B., and Willis, B. C.: Mixed Tumors of the Salivary Glands, Am. Jour. Med. Sc., 1912, cxliii, 656.

COMMENT

What inference may we draw from these two cases? Is there any one etiological factor responsible for the development of these multiple primary malignant tumors in either case, or are they incidentally multiple?

It is well known that malignant disease of the thyroid gland in man and in the dog is more prevalent in goitrous districts than in non-goitrous districts. In Great Britain, where goiter is not prevalent, only seven cases of malignant disease of the thyroid were found in 7,294 necropsies.[29] In Vienna, where goiter is not uncommon, Hinterstoisser[30] found fifty malignant tumors of the thyroid in 18,147 necropsies. On the other hand, in Berne, where goiter is common, Limacher[31] found eighty-two cases of malignant disease of the thyroid in only 7,641 necropsies; thirty-eight of these were carcinoma, while forty-four were sarcomas. Marine and Lenhart[32] have shown from their work on brook-trout that the goiters of fish are entirely due to metabolic disturbances from food and external conditions. They[33] state the following in reference to malignant disease of the thyroid gland: "Goiter in some way favors the development of cancer, just as it favors the development of benign tumors. Cancer developing in an otherwise normal gland is extremely rare. We have never observed thyroid cancer apart from preexisting goiter."

The ordinary goiter in dogs is due usually to a diffuse enlargement of the gland, and rarely to adenomas; Marine and Lenhart assert that fetal and that simple adenomas are never found in dogs. In and about Chicago, where goiters in dogs are very common, carcinoma of this gland is not at all infrequently found.

In both Dogs A and B there is nothing that indicates a preexisting developmental anomaly; presumably the thyroid carcinomas in both cases were preceded by, and indirectly due to, a diffuse hyperplasia, which in turn is no doubt, so far as is known, a manifestation of metabolic disturbance dependent on the water and food.

In Dog A, in addition to the thyroid carcinoma, there are the bilateral adrenal hypernephromas, or better, "mesotheliomas," so far as it has

29. Müller, G. P., and Speese, J.: Malignant Disease of the Thyroid, Univ. Penn. Med. Bull., 1906, xix, 74.

30. Hinterstoisser, H.: Beiträge zur Lehre vom Schildrüsenkrebs, Beitr. z. Chir. Festschrift-Billroth, 1892, p. 287.

31. Limacher: Quoted by Müller and Speese. (See Footnote 29.)

32. Marine, D., and Lenhart, C. H.: Observations and Experiments on the So-Called Thyroid Carcinoma of Brook-Trout and Its Relation to Ordinary Goiter, Jour. Exper. Med., 1910, xii, 311.

33. Marine, D., and Lenhart, C. H.: Pathological Anatomy of the Human Thyroid Gland, THE ARCHIVES INT. MED., 1911, vii, 506.

been rather conclusively shown that renal hypernephromas and adrenal hypernephromas are distinct from each other both embryologically and histologically. These two adrenal tumors have undoubtedly originated from an anomalous embryonal development, since they are bilateral, and are associated with bilateral, congenital, multicystic kidneys. The cavernous hemangioma of the liver is of doubtful embryonal development. There is, then, nothing in common in the etiology of the thyroid carcinoma and of the double adrenal mesothelioma, one being of probable indirect metabolic origin, while the others are from embryonal anlages. Their location does not suggest that they are the result of any one tissue susceptibility, the adrenals being of mesothelial origin, while the thyroid is of ectodermal origin.

In Dog B, besides the carcinoma of the thyroid gland, there is the mixed tumor of the mammary gland, similar in structure to those mixed tumors in the parotid gland. This tumor, like the adrenal tumors in Dog A, without much doubt is of embryonal origin. It is closely allied to the teratomas, having cartilage, myxomatous tissue, endothelial structures and a sarcomatous stroma. The various grades of teratoma and mixed tumors are most frequently found in the ovaries, testes, parotid gland and mammary gland. In Dog B the occurrence of multiple capsular adenomas of the adrenals is significant of an imperfect embryonal development.

Both the malignant tumors in Dog B, then, also are, as in Dog A, very probably of different etiology, the one being due indirectly to metabolic disturbance, and the other, the mixed tumor, being in some way connected with an embryonal anlage. One is of ectodermal and the other of mesodermal origin.

SUMMARY

Multiple primary malignant tumors occur in approximately 0.2 per cent. of all cases of malignant tumors.

Certain of them that originate close together in one type of tissue are indicative of a localized tendency to malignant degeneration.

Others that are essentially bilateral, occurring in the ovaries, testicles, kidneys and adrenals, are indicative of a tissue predisposition, dependent in most instances on an anomalous embryonal development.

Besides these two classes there is another general class of cases, two-thirds of which is composed of multiple primary malignant tumors, the location and arrangement of which is strongly indicative of a system involvement, affecting mainly the reproductive, the gastro-intestinal and the cutaneous systems.

In the other third of this class of cases, the tumors are distributed miscellaneously, and apparently have no common features. The two

cases here reported belong to the latter class, each animal having one tumor dependent indirectly on a metabolic disturbance, and another tumor distinctly of embryonal anlage.

I wish to thank Dr. D. J. Davis for his kind suggestions in the compilation of this paper.

1532 Congress Street.

FATTY INFILTRATION (LIPOMATOSIS) OF THE AURICULOVENTRICULAR BUNDLE OF HIS, WITH SUDDEN UNEXPECTED DEATH *

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CHICAGO

Numerous studies have established a definite relationship between the symptoms usually referred to as Adams-Stokes disease and changes in the auriculoventricular bundle of the heart, the bundle of His. The absence of sufficient information in many of the reports in a recent summary by Bachman[1] led him to base this definite relationship on the evidence in only twenty-four of the eighty-six cases reviewed; in the remainder the details were inadequate for comparison.

In these twenty-four, to which I have added a few[2] not in the number considered by Bachman, the alterations found in the His bundle were as follows:

Condition	Cases
Gumma	7
Fibrosis	7
Calcified plaques	3
Lipomatosis	2
Round celled infiltration	3
Arteriosclerosis of the bundle vessels	2
Tumor	1
Anemic infaret	1
Parenchymatous degeneration	1

From a study of such a table as this it is evident that well-marked examples of the Adams-Stokes syndrome have for their explanation a lesion of the auriculoventricular bundle. A number of careful studies have shown that a complete transverse lesion of the main stem of this conducting system is followed by a total heart-block.

It is possible, however, that when the auriculoventricular bundle possesses alterations only a portion of the symptoms regarded as essential for the Adams-Stokes syndrome are manifested. Beginning or partial involvement of the bundle may lead simply to a lengthening of the inter-

* Submitted for publication Dec. 5, 1913.

* From the Pathological Laboratory of the Rush Medical College.

1. Bachman: A Physiologico-Pathological Study of a Case of Heart-Block Occurring in a Dog as a Result of Natural Causes, Jour. Exper. Med., 1912, xvi, 3.

2. Keith and Miller: Lancet, London, 1906, ii, 1429; Heinecke: Drei Fälle von Adams-Stokes Krankheit, Berl. klin. Wchnschr., 1907, xliv, 1125; Karscher and Schaffner: Ein Fall von Adams-Stokes 'scher Krankheit mit Schwiele im His 'schen Bündle, Berl. Klin. Wchnschr., 1908, xlv, 1266.

systolic period.[3] Or there may be only bradycardia, tachycardia, arhythmia or cyanosis.[4] Furthermore, in a few instances sudden death has occurred without, so far as known, any illness with symptoms leading to even a suspicion of Adams-Stokes disease. Mönckeberg[5] has reported two such occurrences.

The first was diphtheria with sudden death. Mönckeberg does not state at what period in the disease death occurred. No gross changes were found in the myocardium at the post-mortem examination. The auriculoventricular bundle and its many branches when sectioned serially in paraffin and stained by Van Gieson and hematoxylin appeared normal. Using Scharlach R., however, the main stem, both branches and their subdivisions were found to be the site of a distinct fatty change which sharply differentiated this system from the fat-free myocardium.

In Mönckeberg's second example sudden death followed trephining of the skull, as a result of caries of the frontal bone. The myocardium presented fatty changes. In Scharlach R. preparations both divisions of the His bundle stood out in marked contrast due to the greater fatty change that was present in them. Yet there were individual fibers among these unaffected and normal in all respects.

Acute fatty changes similar to these and caused by septicemia, pneumonia, typhoid fever, diffuse bronchitis and chloroform poisoning have been studied by Sapegno.[6] Among other results of the studies of seventy-two hearts he concluded that rapid, unexpected death of an individual, in whom no other anatomic alteration is found, may be due to an acute or a chronic lesion of these peculiar fibers in the heart. He also believes that while fatty changes are often present in both the myocardium and the bundle system together, yet in 50 per cent. of all instances these acute changes affect especially the conducting system.

Similar alterations have also been found by Aschoff[7] in the His bundle. He has not, however, observed any instance in which such a change was responsible for the sudden death.

Marked fatty changes of an *entirely different* sort than those discussed by Mönckeberg, Aschoff and by Sapengo as quoted above, may be very

3. Erlanger: On the Physiology of Heart-Block in Mammals with Especial Reference to Causation of Adams-Stokes Disease, Jour. Exper. Med., 1906, viii, 8.

4. Von Neusser: Disorders of the Respiration and Circulatiton, 1908 (New York), Part 2, p. 18.

5. Mönckeberg: Untersuchungen über das auriculo-ventricular Bundle bei Mann, Jena, 1906, Cases 71 and 104, p. 318.

6. Sapegno: Nuove Ricerche sulla Patologia del Fascia atrioventricolare, Arch. per le Sc. med., 1910, xxxiv, 549.

7. Referat über die Herzstörungen in ihrem Beziehungen zu den Spezifischen Muskelsystem des Herzens, Verhandl. d. Deutschen. patholog. Gesellsch., 1910, xiv, 3.

extensive in the His bundle, as is well shown by the following report of fatty infiltration or replacement of the His bundle by adipose tissue associated with sudden death.

History.—A man 38 years of age, who had always been well, died suddenly. Friends stated that at times he had seizures during which he trembled generally and voluntarily or consciously shook his hands and forearms rapidly. These only lasted a moment or two and there was no loss of consciousness. So far as is known he never sought medical advice.

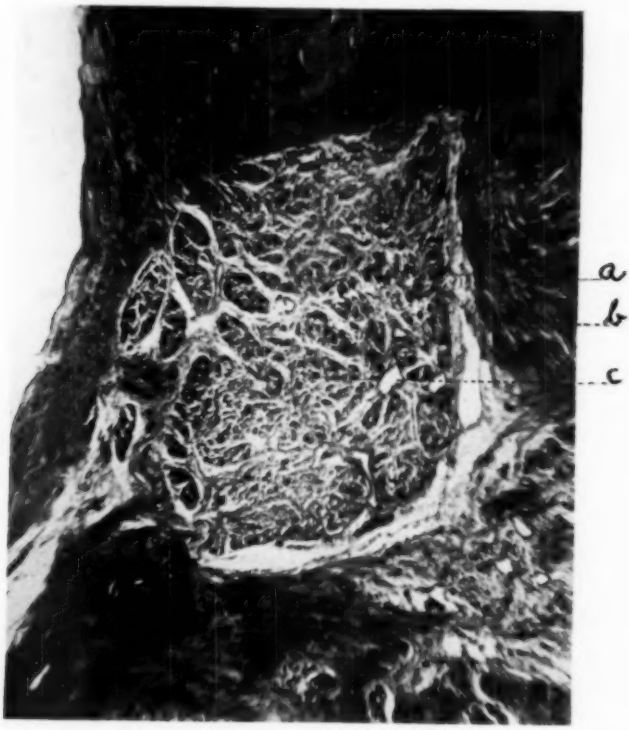

Fig. 1.—A transverse section through the distal portion of the normal node of the His bundle at a point in its passage through the auriculo-ventricular fibrous ring. a. Bundle fibers. b. Fibrous connective tissue surrounding the bundle. c. Bundle vessels.

Necropsy.—The body was that of a powerful, well-nourished white man with no external injuries. There was no excess of subcutaneous adipose tissue. The organs were found to be of normal size and position. There were no gross evidences of disease anywhere. Careful examination of the gastro-intestinal tract failed to disclose any alterations leading to a suspicion that death might have resulted from poisoning, nor did the circumstances attending his death indicate this possibility.

The heart was not hypertrophied and in so far as could be ascertained by gross examination was normal in all respects save for a slight degree of coronary sclerosis and a moderate fibrous myocarditis. There was no abnormal deposit of fat on the outside of the heart.

"There are approximately two small nodules in each coronary artery. The first nodule in each vessel is 1.5 cm. distal to the sinus of Valsalva. The nodules involve the intima of the vessel wall chiefly and the lumen is but slightly lessened in each instance. On tracing the coronary arteries to their terminal endings no occlusions are found. The vessels are not tortuous and the walls are elastic."

Fig. 2.—Adipose tissue in the node. a. Central fibrous body surrounding the node. b. Intact bundle fibers. c. Adipose tissue. d. Bundle vessels.

Portions of both the right and left ventricular walls, the septum and papillary muscles were examined at various levels to determine the amount of fibrosis.

"The septum contains only a normal amount of fibrous connective tissue. The fibrous tissue in the ventricular walls is somewhat increased in amount. At all points this increase is only slight and but few true muscle fibers are replaced. This change is not especially prominent in any portion of either ventricular wall. The amount of fibrosis in the papillary muscles is even less than that observed in the outer ventricular wall."[8]

8. Dr. E. R. LeCount, who conducted the post-mortem examination, was of the opinion that the gross changes in the heart were inadequate to explain death.

The following anatomic diagnosis was made:

"Slight nodular sclerosis of the coronary arteries; slight fibrous myocarditis; slight fibrous mural endocarditis; passive hyperemia of the liver, spleen, kidneys, pancreas and small bowel; petechial hemorrhages in the large and small bowel and in the pleura of the right lung; marked chylangiectasis of the vessels of the small bowel—post-mortem (?); hyperplasia of the tracheo-bronchial lymph-nodes, of the mesenteric lymph glands, of the spleen, of the solitary follicles of the small bowel and of the lymphoid tissue of the pharynx; marked emphysema of both lungs; edema of the pharyngeal mucous membrane; caseous infratracheal lymph-nodes; fibrous patch in the pia of the left frontal lobe of the brain; slight sclerosis of the aorta and of the vessels at the base of the brain; fibrous adhesions between

Fig. 3.—Section distal to that shown in Fig. 2. Two-thirds to three-fourths of the bundle fibers are replaced by adipose tissue in this and adjacent sections. a. Intact bundle fibers. b. Beginning of left ramus. c. Bundle vessels. d. Adipose tissue.

the gall-bladder and the first portion of the duodenum; fibrous pleuritis; small fibrous patches in the anterior mitral leaflet; slight fibrous subepicardial and supra-arterial nodular pericarditis; marked right halux valgus; carious and missing teeth."

Because the gross alterations were so few a study of the His bundle was undertaken. Histological examination was carried out by means of serial paraffin sections of the entire bundle down to and for a considerable distance beyond the

point of origin of the right and left branches. Further study was made of the terminal extensions at various levels in the ventricular walls. Every fifth section was mounted and various stains employed.

In these sections there is a very marked fatty infiltration limited strictly to the auriculoventricular bundle and its branches, the myocardium containing no adipose tissue. This change is moderate in the nodal region, more marked in the main stem. At the point of origin of the right and left branches nearly the entire bundle is absent and in its place there is adipose tissue. Both of these branches and the Purkinje fibers at whatever plane examined present such alterations in varying degree.

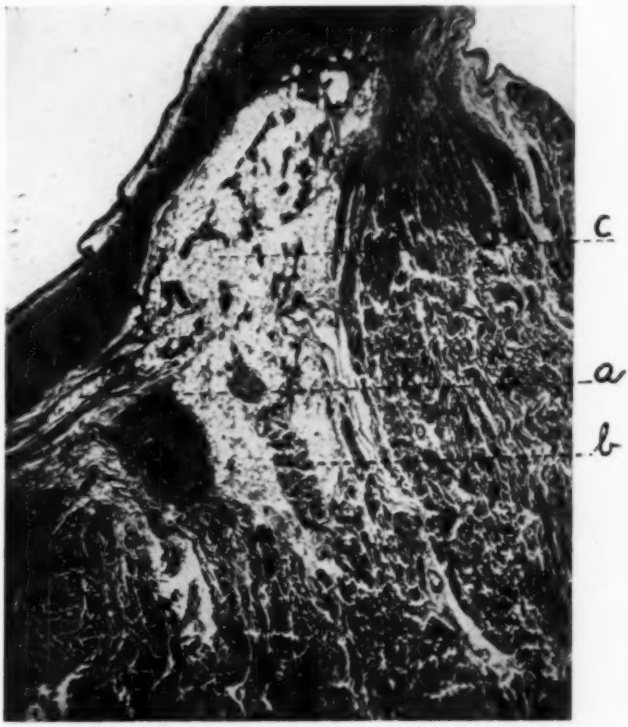

Fig. 4.—Section distal to that shown in Fig. 3. A portion of the left ramus and the beginning of the right ramus are present here. In this section 85 to 95 per cent. of the bundle fibers are replaced by adipose tissue. a. Left branch of bundle. b. Beginning of right ramus. c. Main portion of bundle.

Both the muscle fibers and the connective tissue of the bundle system are replaced by adipose tissue. If that part of the bundle lying between the proximal part of the node and the point of division of the main stem into right and left branches is arbitrarily divided into three segments then approximately 20 per cent. (Fig. 2) of the fibers and connective tissue framework of the first segment of the bundle is replaced by adipose tissue, 65 to 75 per cent. (Fig. 3) of the middle segment and 85 to 90 per cent. (Fig. 4), of the distal segment is similarly

affected. Just distal to the bifurcation of the bundle 50 per cent. of the structure of the right branch is replaced by adipose tissue while at a similar location in the left branch only 10 to 15 per cent. of the fibers are so affected. These alterations are present, as before stated, in the terminal portions of this specific system of muscle fibers throughout their subendocardial course. The adipose tissue, limited sharply to the Purkinje fibers, differentiates this system at a glance from the surrounding myocardium. In fact their location is readily determined with a hand lens or the low power of a microscope and followed from section to section by the adipose tissue-fat holes at such points.

Some of the muscle cells of the Purkinje fibers are normal. Others on cross section show fat globules in their centers. These globules vary in size from small droplets to larger drops which replace a portion of the protoplasm, leaving the

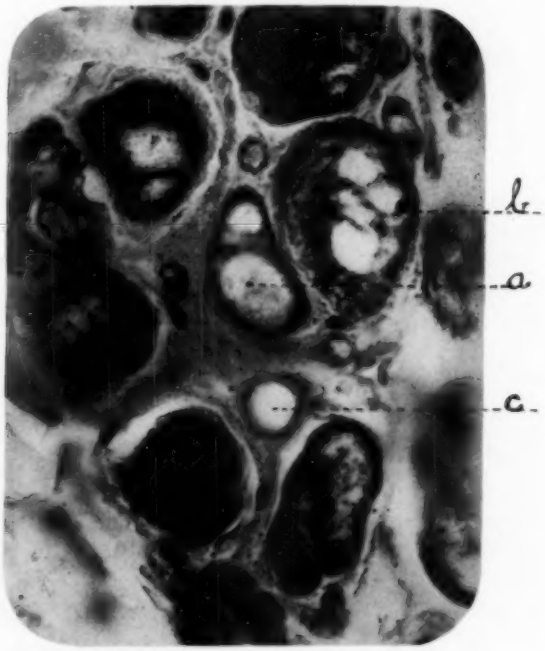

Fig. 5.—Terminal "specific" muscle fibers sectioned across, phosphotungstic acid hematoxylin stain. a. Typical arrangement of fibrillae about the cell periphery. Protoplasm in center of cell replaced by fat. b. Fibrillae dividing cell into fields. Center of fields occupied by fat. c. Entire cell almost entirely replaced by adipose tissue.

fibrillae standing out very sharply about the periphery of the cell (Fig. 5a). Again, the fibrillae may divide the cell into small fields, the center of these fields being occupied by fat droplets (Fig. 5b). Or the muscle cell may be so distended with fat globules that the remaining fibrillae have all been crowded into one corner of the cell, many of them absent. Finally the entire muscle fiber with its fibrillae, cell membrane and surrounding sheath of connective tissue may be entirely absent and its place taken by adipose tissue.

As a rule, this replacement by adipose tissue, lipomatosis, which is quite regularly found in the auriculoventricular bundle system of elderly people is not extensive enough to lead to clinical manifestations, yet Fahr[9] has reported so marked a lipomatosis of the bundle that the Adams-Stokes complex resulted and finally death. Aschoff and Tawara[10] have made a similar observation, but Sapegno[11] states in his second article that they later denied the occurrence of a true Adams-Stokes symptom-complex in this instance.

Sapegno[11] describes a lipomatosis found in the His bundle in the heart of a young girl who died twelve days after recovery from typhoid fever. He is very positive in his statements that death in this instance, which was sudden, was not due to the acute fatty changes in the myocardium which are sometimes observed after typhoid fever. Furthermore, this young girl had a cardiac insufficiency which was present from birth and the lipomatosis of the bundle which he found he regarded as congenital. On account of the absence of other gross alterations or processes of disease in the body, death was attributed to the presence of the very marked lipomatosis of "from the point of division of the main branch into two rami to a point where these again decrease rapidly in size."[12]

He concurs with Mönckeberg in recognizing that there is a tendency toward adiposity of the auriculoventricular system in old age, and that while, as a rule, this adiposity is accompanied by fatty infiltration of the myocardium generally, that the bundle alone may be affected and possess grossly visible fat.

In conclusion, without attempting to predicate that death in this instance was necessarily due to these alterations in the His bundle, it is believed that such an examination as this in instances of sudden death with symptoms of cardiac disease, where there are relatively few gross changes in the heart, should be more frequently made. As has been suggested by other investigators of conditions in the auriculoventricular bundle, the nerves connected with it should also be examined.

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9. Fahr: Cited by Mönckeberg: Berl. klin. Wchnschr., 1909, xlvi, Part 2, p. 45.

10. Aschoff and Tawara: Die Pathologische-anatomische Grundlagen der Herzschwache, Fisher, Jena, 1906.

11. Sapegno: Ricerche sulla patologia del fascia atrio-ventricolare, Arch. per le sc. med., 1910, xxxiv, 143.

12. The original is as follows: "Il cusicinetto adiposo si mantiene sempre di una massa notecole fino alla divisione del f. nei suoi due rami, al qual livello diminuisce rapidamente di volume e cessa quasi del tutto."

BLOOD-PRESSURES

THEIR RELATION TO EACH OTHER AND TO PHYSICAL EFFICIENCY *

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In this communication we desire to record the blood-pressure findings in a total of 742 males with particular reference to the diastolic and pulse pressures; also the relations between blood-pressure and physical efficiency.

METHODS

In these blood-pressure readings we used a mercury manometer of the usual type with 12 cm. cuff, and we made our determinations by the auscultatory method.

The maximum pressure was determined in all cases at the first sound. The minimum pressure in Series A was read at the time of disappearance of all sounds (fifth phase); and in Series B, more accurately at the point of the last clear sound preceding the final dull tones. This is known as the fourth phase. Obviously, then, we get a reading somewhat higher when we make our readings at the final sharp tone than if we wait for the disappearance of all sounds. The difference may be as much as 10 mm. and usually in the neighborhood of 5 mm. This difference, while noteworthy, is not sufficiently great to detract from the actual value of our figures for the minimum blood-pressure in Series A in the manner in which we use them.

The subjects in this study were students in their usual health, most of them between 15 and 25 years of age. While our records include the readings in both the erect and horizontal posture, the accompanying tables and figures refer only to the readings in the erect, the effect of change of posture on the arterial and venous pressures having been previously studied by us.[1]

The method used in estimating the physical efficiency in this work is the one known as the "intercollegiate standard." It consists of adding the strength of back, plus strength of legs, plus strength of right and left forearms, plus lung capacity divided by twenty, plus body-weight divided

* Submitted for publication Jan. 6, 1914.

* From the Department of Student Health, Carnegie Institute of Technology.

1. Barach, J. H., and Marks, W. L.: Effect of Change of Posture without Active Muscular Exertion on the Arterial and Venous Pressures, ARCHIVES INT. MED., 1913, xi, 485.

by ten. The last figure obtained is multiplied by the number of times the subject pulls up and dips his body by the strength of his arms and shoulder muscles. This gives us a very fair estimate of the individual's physical condition. For one to show a high total strength he must possess a good musculature, good coordination, an efficient circulatory and respiratory system, one which will respond properly and maintain itself during the effort required by the test.

MINIMUM PRESSURES

In the accompanying tables it will be noted that we do not give the average height of the blood-pressure readings of an entire series of cases, but rather do we give the actual number of cases which occurred at the various heights. We believe this to be more accurate and leading to truer conclusions.

TABLE 1.—AGE DISTRIBUTION IN A SERIES OF 552 CONSECUTIVE CASES

Age, Years	Cases
15 to 17	27
17 to 19	200
19 to 21	202
21 to 23	71
23 to 25	31
25 to 27	12
27 to 29	6
29 to 31	1
Over 31	2
Total	552

Maximum Pressure.—As heretofore stated, the maximum pressure was read at the first sound—by the auscultatory method. In 656 cases the distribution was as shown in Table 2.

TABLE 2.—DISTRIBUTION OF MAXIMUM PRESSURE IN 656 CASES

Mm. Hg.	Cases
90-100	7
100-110	23
110-120	112
120-130	204
130-140	153
140-150	95
150-160	45
160-170	14
170-180, 180-190, 190-200	3
Total	656

Out of these 656 cases, there are 594 under 150 mm. Hg.; these comprise 90 per cent. of the entire series. It has been our experience that just about 10 per cent. of the men come in presenting a blood-pressure considerably higher than normal at their first examination, but at a

subsequent examination it is found to be much nearer the normal level. This undoubtedly is due to the psychic effect of the examination.

Minimum Pressure, Series A.—Here the pressure was read by the auscultatory method at the disappearance of all sounds, with the results shown in Table 3.

TABLE 3.—MINIMUM PRESSURE READ BY THE AUSCULTATORY METHOD AT DISAPPEARANCE OF SOUNDS

Mm. Hg.	Cases	
30- 40	1	
40- 50	2	
50- 60	4	
60- 70	20	327 Cases = 96 %
70- 80	82	
80- 90	140	
90-100	78	
100-110	9	
110-120	1	
120-130	1	
Total	338	

The majority of these, 96 per cent., had a minimum pressure under 100 mm. Hg.

Minimum Pressure, Series B.—In these cases the point of the minimum pressure was read at the last clear sound preceding the final dull tones (Table 4). It is now generally agreed that this is the exact point of the minimum pressure.

TABLE 4.—MINIMUM PRESSURE READ AT THE LAST CLEAR SOUND

Mm. Hg.	Cases	
40- 50	1	
50- 60	4	
60- 70	12	273 cases or 87 %
70- 80	41	
80- 90	94	
90-100	121	
100-110	27	
110-120	9	
120-130	3	
Total	312	

In this series, in which the point of minimum pressure is read earlier than in Series A, we find that over 87 per cent. of the cases present a minimum pressure under 100 mm. Hg, and that 256 cases, or 82 per cent., occur between the points of 70 mm. and 100 mm. Hg.

We see, then, that when the minimum pressure is read at the fourth phase, 87 per cent. of the cases are found to be not over 100 mm. Hg, while at the end of the fifth phase 96 per cent. of the cases do not exceed 100 mm. Hg.

In Series B, in which the pressure was read at the fourth phase, the 13 per cent. which had a maximum pressure of over 100 mm. were reexam-

ined. We then found that the first was only a temporary response to the psychic effect of the examination and that in only two cases did the minimum blood-pressure exceed 100 mm., one showing a minimum blood-pressure of 105 and the other 102 mm. Hg.

Minimum Pressure in All Cases.—If we allow for clinical purposes that the difference between the end of the fourth and fifth phase in a large series of cases such as this one is a negligible factor, by combining Series A and Series B we get the results shown in Table 5.

TABLE 5.—MINIMUM PRESSURE IN ALL CASES

Mm. Hg.	Cases	
30- 40	1	
40- 50	3	
50- 60	8	
60- 70	32	600 cases or 92 %.
70- 80	123	Not over 100 mm. Hg
80- 90	234	
90-100	199	
100-110	36	
110-120	10	
120-130	4	
130-140	..	
Total	650	

Pulse-Pressures.—In Series A and B we have pulse-pressure readings in 629 cases. The normal variation in the size of the pulse-pressure is seen to be quite marked.

TABLE 6.—PULSE-PRESSURES IN SERIES A. MINIMUM PRESSURE READ AT THE FIFTH PHASE

Mm. Hg.	Cases
10-20	9
20-30	30
30-40	68
40-50	76
50-60	62
60-70	43
70-80	17
80-90	7
Total	312

TABLE 7.—PULSE-PRESSURE IN SERIES B. MINIMUM PRESSURE READ AT THE FOURTH PHASE

Mm. Hg.	Cases
5- 10	1
10- 20	11
20- 30	45
30- 40	79
40- 50	79
50- 60	53
60- 70	25
70- 80	18
80- 90	5
90-100	1
Total	317

Tables 6, 7 and 8 show clearly that we may hold the usual pulse-pressure as ranging between 20 and 70 mm. Hg, in healthy persons of the ages here referred to.

TABLE 8.—PULSE-PRESSURE IN SERIES A AND B COMBINED

5- 10	1	
10- 20	20	
20- 30	75	560 cases or 88%. Between 20 and 70 mm. Hg.
30- 40	147	
40- 50	155	
50- 60	115	
60- 70	68	
70- 80	35	
80- 90	12	
90-100	1	
Total	629	

RELATION BETWEEN THE PULSE-PRESSURE AND DIASTOLIC PRESSURE

Strassburger[2] attempted to find a blood-pressure quotient by dividing the pulse-pressure by the maximum pressure, but that has been shown to be erroneous. It has recently been stated by Stone[3] that the pulse-pressure in the normal individual is equal to 50 per cent. of the diastolic pressure, and that for clinical purposes we may assume that, when the pulse-pressure is over 50 per cent. of the diastolic pressure, we are dealing with cardiac overload. If this theory could have been proved, it would have been an important advance in our clinical work.

We set forth here the findings in 742 cases. Series A has its slight error on account of the minimum pressure having been read at the fifth phase, while in Series B this element is eliminated. The figures represent the percentage relation of pulse-pressure to diastolic pressure. Our formula is D.P.:P.P.::100:×.

TABLE 9.—SERIES A. MINIMUM PRESSURE READ AT FIFTH PHASE

Per Cent.	Cases			
10- 20	10			
20- 30	24			
30- 40	48			
40- 50	49	108 cases, 30%	201 cases, 60%	264 cases, 70%
50- 60	59			
60- 70	45			
70- 80	39			
80- 90	23			
90-100	14			
100-110	16			
110-120	2			
120-130	1			
130-140	5			
Total	335			

2. Strassburger: Arch. f. klin. med., 1905, lxxxv.

3. Stone, Willard, J.: The Clinical Significance of High and Low Pulse-Pressures with Special Reference to Cardiac Load and Overload, Jour. Am. Med. Assn., Oct. 4, 1913, p. 1256.

TABLE 10.—SERIES B. MINIMUM PRESSURE READ AT THE FOURTH PHASE

Per Cent.	Cases			
5- 10	2			
10- 20	8			
20- 30	44			
30- 40	63			
40- 50	73	141 cases, 34%	260 cases, 63%	333 cases, 81%
50- 60	68			
60- 70	56			
70- 80	29			
80- 90	32			
90-100	11			
100-110	13			
110-120	1			
120-130	2			
130-170	5			
Total	407			

In Series B, in which the pulse-pressure is smaller than in Series A, we note that a greater number of cases occur in the lower percentages. In both A and B we may note that the greatest number of cases do occur near the 50 per cent. mark, and if we were to strike an average it would be close to 50 per cent.; yet this would be far from representing the actual truth. These tables show that there is a wide range both above and below the 50 per cent. mark in normal individuals. Our findings here would warrant only a statement that the pulse-pressure equals from 20 to 80 per cent. of the diastolic pressure in about 75 per cent. of the cases. One objection may be offered to our deductions, and that is the comparative youth of the subjects. Considering the age, the physical development, the height of the blood-pressures, and in the light of our previous observations on older subjects, we incline to believe this objection a negligible factor, and that our findings here are representative for normal persons up to middle life. Other observations on older individuals in health and in various disease conditions with which we expect to deal in another paper, will bear out this point.

RELATION OF TOTAL STRENGTH TO BLOOD-PRESSURES

We have pointed out previously[4] that there is no constant relation between blood-pressures and total strength. In Table 11 we show that there is no definite relation between the pulse-pressure per centage of diastolic pressure and circulatory efficiency, such as is indicated by the general physical efficiency.

The upper 146 cases give a pulse-pressure equal to 56 per cent. diastolic pressure, while the lower 150 cases (excluding the last three) give

4. Barach, Joseph H.: Physiological and Pathological Effect of Severe Exertion (the Marathon Race) on the Circulatory and Renal System, THE ARCHIVES INT. MED., 1910, v, 382.

a pulse pressure equal to 61 per cent. of diastolic pressure, showing that there is no relation between the total strength and pulse-pressure per cent. of diastolic pressure.

It is particularly worthy of note that the man who showed the highest total strength (1724), had a pulse-pressure equal to 100 per cent. of the diastolic pressure. This man certainly had no evidence of cardiac overload. Also that one subject whose strength was only 651 (the fourth lowest of the 344 cases), showed a pulse-pressure equal to 80 per cent. of the diastolic pressure.

TABLE 11.—THE RELATION OF TOTAL STRENGTH TO BLOOD-PRESSURES

Total Strength	Cases	Av. Str.	Average Max. P.	Average Min. P.	Average P. P.	Average P. P. %
400- 500	1	477	117	75	42	56
400- 500	2	445	134	82	50	62
600- 700	1	651	126	70	56	80
600- 700	5	860	129	66	44	54
600- 700	3	647	121	80	41	54
700- 800	5	774	129	88	41	47
800- 900	5	860	129	66	44	54
800- 900	10	865	123	75	47	64
200- 900	35	871	126	84	41	51
900-1,000	3	927	130	83	46	59
900-1,000	19	950	126	81	42	53
1,000-1,100	28	1,045	121	78	42	51
1,000-1,100	4	1,093	117	83	33	45
1,000-1,100	25	1,048	138	67	51	66
1,100-1,200	14	1,161	123	84	39	48
1,100-1,200	34	1,152	130	84	45	54
1,100-1,200	27	1,148	124	75	46	66
1,200-1,300	4	1,243	136	86	49	57
1,200-1,300	22	1,250	135	83	50	66
1,200-1,300	28	1,242	127	80	45	58
1,300-1,400	5	1,331	120	79	40	52
1,300-1,400	9	1,331	135	86	47	55
1,300-1,400	13	1,347	121	76	44	63
1,400-1,500	5	1,456	133	89	44	50
1,400-1,500	12	1,437	137	85	50	60
1,400-1,500	8	1,465	128	76	50	66
1,500-1,600	2	1,566	121	85	36	42
1,500-1,600	8	1,542	133	80	58	73
1,500-1,600	4	1,537	129	84	45	54
1,600-1,700	1	1,633	132	70	62	88
1,600-1,700	1	1,658	115	68	47	69
1,700-1,800	1	1,724	140	70	70	100
Total.....	344					

Comparing the weak and strong halves of the series, which is representative of the subjects who are more likely and those who are least likely to have circulatory inefficiency and cardiac overload, we see that the pulse-pressure percentage of diastolic pressure can offer us no reliable index.

In a former work[4] it was shown that the size of the pulse-pressure is influenced by the systolic pressure, and that the systolic pressure is much more responsive, even to slight influences, than is the diastolic

pressure. We must also take into this consideration the fact that the unit of diastolic pressure has a greater value than the unit in systolic pressure.

As time goes on and our observations accumulate and are being interpreted, we believe that more and more importance will be attached to the height of the minimum pressure, and that the height of the maximum pressure will be considered of lesser clinical import than heretofore. Certainly the maximum pressure alone is of no value excepting as a starting-point for a guess as to the activity of the circulatory system.

SUMMARY

1. In 90 per cent. of a series of 656 healthy young men the maximum blood-pressure was under 150 mm. Hg. It would be still lower if we could eliminate psychic effect.

2. In 96 per cent. of a series of 338 cases the minimum pressure when read at the fifth phase did not exceed 100 mm. Hg.

3. In 87 per cent. of a series of 312 cases the minimum pressure, when read at the fourth phase, did not exceed 100 mm. Hg.

4. On reexamination of the 13 per cent. in the series of 312 cases, we found that 99.4 per cent. had a minimum blood-pressure not over 100 mm. Hg.

5. In 92 per cent. of the total 650 cases the minimum pressure did not exceed 100 mm. Hg at the time of the first examination.

6. In 88 per cent. of a series of 629 cases the pulse-pressure ranged between 20 and 70 mm. Hg.

7. There is no constant relation between the pulse-pressure and the diastolic pressure. In 75 per cent. of a series of 742 cases the pulse-pressure comprises anywhere from 20 to 80 per cent. of the diastolic pressure.

8. There is no relation between physical efficiency, which also means circulatory efficiency, and pulse-pressure percentage of diastolic pressure. In a series of 344 cases, the poorer half gave practically the same pulse-pressure to diastolic pressure percentage as the stronger half, with their better circulatory system.

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THE MECHANISM OF CARDIAC DISPLACEMENTS IN PULMONARY TUBERCULOSIS *

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Monographs on tuberculosis which devote considerable space to the physical diagnosis of this disease usually omit a discussion of cardiac displacements which are so frequently encountered in chests affected by infiltration, fibrous degeneration, collapse, shrinkage and cavitation of pulmonary tissue. Some mention is occasionally made of dextrocardia as liable to occur in extensive right-sided lesions, but minor degrees of displacement, which are so frequently taking place, are altogether forgotten. Some clinicians, however, have observed that dislocation of the heart occurs in pulmonary tuberculosis more often than is generally appreciated. Turban[1] said that a displacement of the cardiac dulness several centimeters to the right, with or without displacement of the heart, is such a frequent symptom of moderate contraction of the right apex that he considers it a typical and cardinal symptom of right apical disease of some standing, and that it may be seen in many cases before the appearance of tubercle bacilli in the sputum.

In their work on fibroid diseases of the lung, Sir Andrew Clark, Hadley and Chaplin[2] show that of forty-five cases of pulmonary fibrosis, thirty-four had cardiac displacements from a half to 3 or 4 inches out of its normal place. Similar conditions were found by these authors in cases of fibroid phthisis.

In this country Pottenger[3] has given the subject of cardiac displacement in tuberculosis considerable attention. He found dislocation of the heart in some form and to some degree in all cases where either a lessening or increase in the volume of the lung occurs. In another paper[4] he gives the following statistics as to its frequency: Of 162 hearts examined, 58 were in practically the normal position, 27 were displaced to the right and 77 were displaced to the left. Of the first-stage cases

* Read before the Section on Medicine of the New York Academy of Medicine, Oct. 21, 1913.
* Submitted for publication Nov. 6, 1913.

1. Turban, K.: Diagnosis of Tuberculosis of the Lung, London, 1906, p. 81.
2. Clark, Hadley and Chaplin: Fibroid Diseases of the Lung, London, 1894, pp. 157, 171.
3. Pottenger, F. M.: Displacements of the Heart and Diaphragm in Pulmonary Tuberculosis, Interstate Med. Jour., 1911, xviii, 605.
4. Pottenger, F. M.: The Effects of Tuberculosis on the Heart, THE ARCHIVES INT. MED., 1909, iv, 306.

one was displaced and 10 were in normal position; of the second-stage cases, 4 were displaced and 17 were in normal position, and of the third-stage cases, 99 were displaced and 31 were in the normal position.

In a clinical study of 2,344 cases of tuberculosis made at the Phipps Institute,[5] it was found that the heart was displaced in but 57 instances: 12 times downward, 31 times to the left and 14 times to the right; of the last group, 5 were cases of complete dextrocardia. On the other hand, Lawrason Brown[6] finds that while in the incipient stage the heart

Fig. 1.—Cavity in left upper lobe; thickened pleura at left base; heart displaced to left and downward. Aorta and trachea also dislocated.

is rarely appreciably displaced, in many patients in moderately advanced stages the ordinary methods of exploration show some changes in the position of the heart. From roentgenographic studies, C. L. Leonard[7] found in a series of 100 cases of tuberculosis 26 displacements of the heart and aorta; in 17 it was displaced to the right, in 4 to the left,

5. Norris, G. W.: Ann. Rep. Phipps Institute, 1906, ii, 235.

6. Brown, Lawrason: The Heart in Pulmonary Tuberculosis, Am. Jour. Med. Sc., 1908, cxxxvi, 819.

7. Leonard, C. L.: Compensation by Displacement of the Thoracic Viscera in Pulmonary Tuberculosis, Med. Rec., 1912, lxxxi, 1.

and in 5 a rotation took place with an upward displacement of the heart and aorta, so that the heart assumed an anteroposterior position. Leonard is of the opinion that marked alterations in the position of the intrathoracic viscera occur in the earlier stages of tuberculosis without visible changing of the excursion of the thoracic wall. Similarly, Francine† found that in many cases of phthisis the heart as well as the aorta, are displaced. He found it in 37 per cent. of cases, and is of the opinion that dislocation to the right is more frequent than to the left. When the pulmonary lesions are of fairly symmetrical character on both sides the heart is more commonly displaced to the right than to the left, according to Francine.

In a recent paper Felix Oeri[8] reports 413 cases of tuberculosis in which the position of the heart was carefully studied. He found that in 43 per cent. of right-sided lesions and 82 per cent. of the left-sided lesions the heart was displaced, or more or less shifted to the affected or more affected side. It appears from Oeri's investigations that dislocations are more likely to occur toward the left side, a view already expressed by Lawrason Brown.[6] This is not because left-sided lesions are more frequent—in fact, they are not—but for anatomical reasons to be discussed later on. Ruedinger,[9] on the other hand, states that dislocations of the heart in phthisis is more frequently directed toward the right side than to the left. Cases of tuberculosis of the right lung in which no cardiac dulness can be discerned to the left of the sternum are not rare. He explains it by the fact that the right lung is the larger lung, and its force of retraction is more powerful, so that traction on the mediastinum will be more effective when pulling it out of its normal location than retraction of the smaller left lung. On the other hand, Lawrason Brown points out that it is readily seen that the displacement of the heart may be much more pronounced when the right lung is affected, for the displacement is most often associated with contraction of one lung. In right apical lesions of some standing, even when the physical signs are slight, the right border of the absolute cardiac dulness may be found ¾ inch or more to the right. Brown states, however, that marked displacement of the heart occurs much more frequently to the left than to the right, owing, possibly, to the fact that the tension, when the left lung contracts, is exerted more directly on the heart. For these reasons a very frequent displacement of the heart is upward and slightly out-

† Francine, A. P.: The Effects of Tuberculosis on Intrathoracic Relations, Am. Jour. Med. Sc., 1910, cxxxix, 732; Intrathoracic Displacements in Pulmonary Tuberculosis, Bull. Johns Hopkins Hosp., 1910, xxi, 244.

8. Oeri, Felix: Herzverschiebung bei Lungentuberkulose, Beitr. z. Klin. d. Tuberk., Brauer's, 1913, xxvi, 123.

9. Ruedinger, E.: Die Organverlagerung bei Phthise, Beitr. z. Klin. d. Tuberk., Brauer's, 1910, xvii, 151.

ward. The heart, however, may be so greatly displaced to the left, following contraction of the left lung, or pneumothorax, or pleuritic effusion on the right, that the apex may be beyond the left anterior axillary line or in the third intercostal space.

My own experience with tuberculous patients is in agreement with that of Pottenger, Brown and Oeri. In a large number of cases of phthisis in which I looked for the position of the heart while examining the thorax, I found the heart dislocated in such a large proportion that

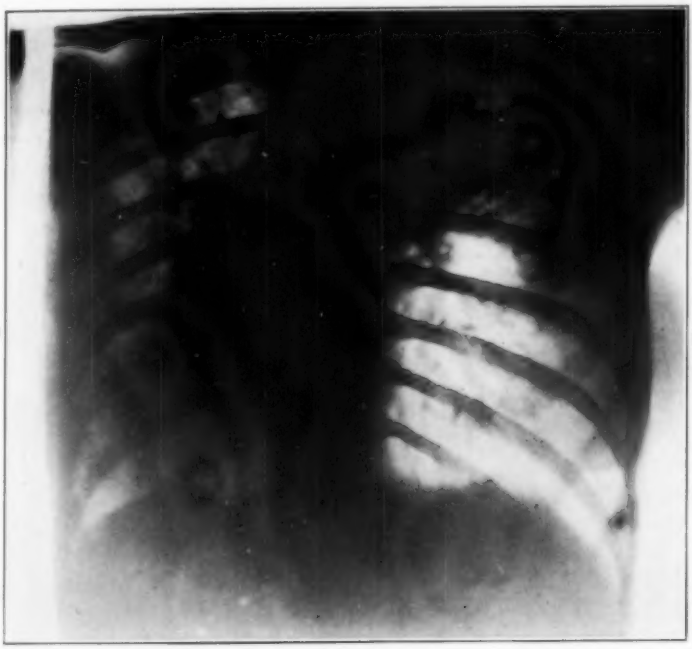

Fig. 2.—Cardiac displacement to the left and upward; bilateral pulmonary lesion with cavity in left upper lobe. Note dislocation of the aorta to the left.

I wonder why text-books do not mention it, and why most clinicians overlook it. In advanced cases of tuberculosis it is exceptional to find the heart in its normal place. It appears, however, that even pathologists have overlooked this fact, or at least have not taken note of it, perhaps because post-mortem conditions do not show vividly the true location of the heart and its relations to the surrounding lungs, especially in minor degrees of displacement. Leonard[7] mentions a pathologist who did not believe that displacements could occur so frequently in the earlier stages of the disease; but since his attention was drawn to it, he found dislo-

cations very frequently at necropsies. It is only since roentgenography has become a routine method of examination in these cases that the displacements of the heart in tuberculosis are being appreciated. It seems to me that by determining the location of the heart, we can, as a rule, determine in which side the tuberculous lesion is located, or in bilateral lesions which side is the older or more serious lesion, that is, accompanied by destruction of lung-tissue and shrinkage.

Of 115 consecutive cases of pulmonary tuberculosis in which within the last three months I have taken notes on the location of the heart, I found that in 58, or 50 per cent., the heart was dislocated. Of 85 instances with early lesions 31, or 36 per cent., showed cardiac displacements. Of these 22 were displacements to the left and 9 to the right. In other words, 70 per cent. of the displacements were toward the left in early and second-stage cases of tuberculosis. Of 29 far-advanced cases, 27 showed cardiac dislocation, of which 15 were to the left and 12 to the right. Here, again, we have 55 per cent. of displacements to the left.

In the tuberculosis ward of Montefiore Home I found that among 18 far-advanced cases with right-sided lesions, or in which the lesion was more extensive in the right side, 14 showed dislocations to the right and 4 to the left, and in one the heart was in its normal location. Of 19 left-sided lesions, or lesions more extensive on that side, there were 15 displacements to the left, one to the right; in one instance there was no displacement at all. Here the displacements were about equal between the two sides, and, with some exceptions, the shifting of the heart was toward the more affected side. In the cases which did not follow this rule, we always found a reason for the anomaly to be explained later on.

The mechanism of these dislocations of the heart is an interesting topic for study. Experience with intrathoracic tumors, aneurysms, pleural effusions and pneumothorax teaches that the heart is usually displaced toward the healthy side in these cases. While during the course of pulmonary tuberculosis we often encounter cardiac displacements of this kind, as in pleurisy, pneumothorax, etc., yet I do not intend to speak about them in this paper. What concerns us here are displacements in which the heart is displaced toward the affected side, *par attraction*, some French writers call it. In the course of pulmonary tuberculosis, especially in cases running a chronic course, the elastic lung-tissue in the affected region is replaced by fibrous tissue. The lung thus loses its elasticity to a great extent, and its motility suffers greatly. Shrinkage is another feature, thus making room for any intrathoracic organ that may adjoin the affected part. In cases in which there is

also vicarious emphysema of the opposite healthy lung—and they are not at all rare—the mediastinum is pushed toward the affected side. Thus in many cases of pulmonary tuberculosis we have in the chest a *vis a tergo* and a *vis a fronte* both effective in displacing the heart toward the affected side.

Within the pericardium the heart is free and smoothly movable; otherwise it could not pulsate regularly and rhythmically. The pericardium is connected above with the deep cervical fascia by a prolongation of

Fig. 3.—Tuberculous pleurisy and cavitation of left lung; heart displaced to the left and downward; apex-beat in left axillary line.

the fibrous portion through the sheaths over the great vessels. Two bands of fibrous tissue—known as the sternopericardial ligaments—connect the front of the pericardium above and below with the posterior surface of the sternum. Below, the pericardium is connected with the central tendon of the diaphragm closely and intimately. It is also firmly bound to the caval openings, but loosely attached to and easily separable elsewhere. If its oblique position from right to left, as well as its strong attachment to the diaphragm are borne in mind, it is clear that it requires great force to move the heart to the right, while to the left

it is more easily shifted. When either traction from the left side or pushing from the right side occurs, and especially when both forces are operative, the only resistance to be overcome is the upper attachment to the great vessels which is yielding, as is evident from the frequent dislocation of the aorta, trachea and even the larynx in cases of phthisis. But when the forces involved are effective in displacing the heart to the right, its intimate attachment to the diaphragm has also to be overcome. It is for this reason that dislocations to the right are more often seen in far-advanced cases of phthisis, especially such as are complicated by, or which follow, adhesive pleurisy; while dislocations to the left may take place in the early stages of the disease.

That the base, in spite of its attachment to the great vessels, is more movable than the apex of the heart, has been proved experimentally and also by roentgenographic studies of cases of pleural effusion by Bard,[10] Pitres,[11] Sallé[12] and many others. It has been found that when fluid is injected into the left pleura there is no displacement of the heart till at least 1,000 c.c. are injected, and only then the heart moves a little to the right, but no more than 2 or 3 cm. When the injection of fluid is continued, the apex hardly moves, held as it is firmly by the central tendon of the diaphragm, but the base does shift to the right, and the whole body of the heart is moved forward, nearer to the anterior chest wall. In cases of left-sided pleurisy with effusion, Carrière[13] has found confirmatory evidence through roentgenographic studies. An effusion of from 700 to 1,000 c.c. does not at all displace the heart; the apex remains in its normal place, and only when the patient assumes an erect posture, or reclines on his right side, does the apex move from 2 to 4 cm. to the right, nearing the median line. In effusions of from 1 to 3 liters the long axis of the heart becomes vertical, the apex is lowered and shifted to the median line; and with an effusion of 3 liters it is moved as far as the xyphoid appendix. When the effusion exceeds this quantity, the heart is shifted completely to the right, but it is not swung over, retaining as it does the normal direction of its long axis from right to left and from above downward—the apex remains at the xyphoid appendix and the base is shifted to the right hemithorax. Torsion is never observed.

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10. Bard: Refoulement du coeur à droite et dextrocardie congénitale, Lyon méd., 1892, lxxi, 583; 1893, lxxii, 1; Refoulement du coeur à droite dans les épanchements pleuraux, Méd. moderne, 1897, viii, 185.

11. Pitres: Les signes physiques des épanchements pleuraux et en particulier sur les deplacements du coeur, Arch. clin. de Bordeaux, 1896, v, 1, 65, 241.

12. Sallé De déplacements du coeur par les épanchements pleuraux gauches au point de vue experimental et clinique, Thèse de Paris, 1908-1909.

13. Carrière: Dèplacement du coeur et des organs abdominaux dans les épanchements pleuritiques, Presse méd., 1898, vi, 349.

Of course, it is often different with cases of phthisis with strong fibrous bands and pleuropericardial adhesions which immobilize either the apex or the base and keep it in that position. In case the base is immobilized, the apex may move through traction by some other fibrous bands, and the heart assumes a vertical position within the chest, or the axis may be reversed, running from left to right; but this is exceedingly rare. According to the amount, density, location and direction of the adhesions and pulmonary retraction that may be present in a given case of phthisis, the heart may be dislocated upward or downward, to

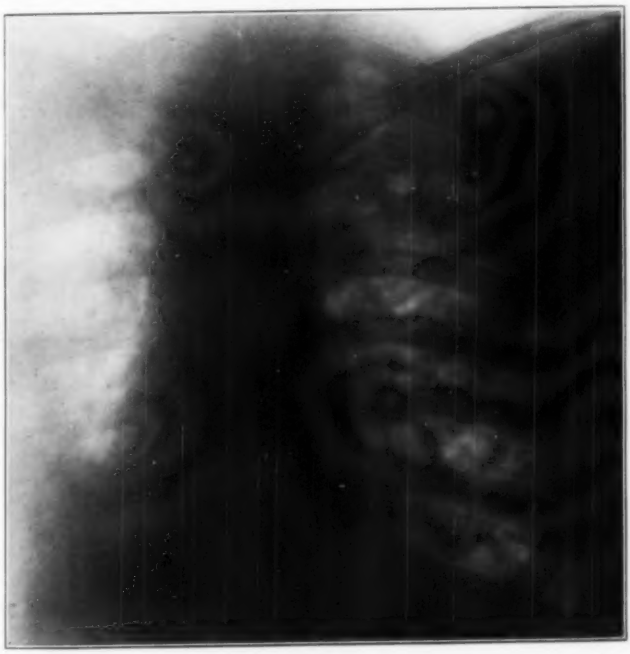

Fig. 4.—Cardiac dislocation to the right with rotation on its sagittal and vertical axes; bilateral pulmonary lesion; adhesive pleurisy in right hemithorax.

the right or to the left. The apex may be lifted up to an extent as to bring the heart in a horizontal position resting on the elevated diaphragm. Clinical experience shows many of these anomalous dislocations when we look for them.

The usual location of tuberculous lesions is at the apices, and retraction and scar formation occurs more often in the upper part of the lungs and pleura, thus pulling the heart upward by fibrous bands running to its base from the affected lung or pleura. When the traction comes

from the left upper lobe the heart easily yields and moves upward and to the left; when traction is exerted from the right apex, the effect depends on the extent and kind of lesion in the lung. In cases with strong fibrous bands running from the right pleura to the pericardium, especially when there is also cavitation in the right lung making place for its reception—here also Nature abhors a vacuum—and the left lung is emphysematous, encroaching with its bulk on the right side of the thorax, pushing the mediastinum toward the right, all obstacles are overcome more or less and the heart moves to the right side; in extreme cases we may find under these circumstances complete dextrocardia with the apex-beat to the right of the sternum. Shrinkage of the lung takes place in both a horizontal and a vertical direction, and thus not only the mediastinum, but also the diaphragm is often dislocated. Strictly speaking, elevation of the diaphragm in one side will push the heart upward and to the opposite healthy side; but inasmuch as fibrosis and retraction of the lung not only pulls up the diaphragm vertically, but retracts the lung horizontally, the heart is usually attracted toward the affected side. When there is a pulmonary cavity and emphysematous lung on the opposite healthy side, it is evident that the dislocation will be toward the affected side.

In tuberculosis the position of the heart is consequently greatly influenced by the position of the diaphragm. An elevation of the right half of that muscle tends to shift the heart to the left; elevation of the left half of the diaphragm first raises the apex of the heart, bringing it into a horizontal position, and when the height of the left half of the diaphragm greatly exceeds that of the right half, there may occur a dislocation of the heart to the right. When pleuropericardial adhesions are strong and dense they may pull the heart to the left and upward, as we see in many cases of phthisis, especially those following adhesive pleurisy of the left side.

Older writers spoke of a form of cardiac dislocation in which that organ, fixed at its base by the great vessels, was swung over to the right side like a door on its hinges. This has been found erroneous, as has been shown in the excellent anatomical, clinical and experimental studies of Bard,[10] Pitres,[11] Sallé[12] and others; but we do know that rotation on its sagittal and vertical axes often does take place. In the normal position of the heart the left ventricle is nearer the chest wall than the right, which is turned to the back. As Oeri[8] points out, traction exerted on the right side brings the right ventricle nearer the chest wall, while the apex is moved away from it; traction on the left side may increase the obliquity of its position and pull the heart completely toward the left. Cavitation in the left upper lobe, combined with fibrous bands running between the pleura and pericardium, dislocates the heart not only

to the left but also upward, and this is greatly assisted by the upward displacement of the diaphragm, as was already mentioned. It must also be borne in mind that the left half of the diaphragm is easily movable.[14] Traction toward the right, if not very strong, may turn the heart on its sagittal, and at times on its vertical axis, and as a result we find an increase in the dulness to the right of the sternum, because the base of the heart has approached the chest wall without much shifting, while the apex, moved as it is backward, cannot be found on inspection and percus-

Fig. 5.—Shifting of heart to the right with rotation on its sagittal axis in an extensive right-sided tuberculous lesion.

sion. This explains some of the cases of vertical hearts which we find so often in roentgenograms when examining advanced cases of tuberculosis.

When we have two forces combined, as in traction on the right side due to dry pleurisy with massive adhesions, pulmonary fibrosis, long-standing tuberculous pleurisy with formation of false membrane, pleuro-pericardial adhesions which immobilize the heart and fix it in an abnormal position, and an emphysematous lung in the left hemithorax

14. Sahli: Diagnostic Methods, Second American edition, p. 251.

making place for itself by encroaching across the sternum to the right, we may find complete and permanent dextrocardia. In these cases there is no rotation of the heart with swinging all the way around on its point of fixation at the great vessels, as was formerly thought. This would be incompatible with life. As has been shown by recent experimental investigations at the necropsy-table and with the Roentgen ray, the heart is in these cases pushed over to the right hemithorax *in toto*, the base is usually displaced to the same extent as the apex, and it retains its natural oblique position in the chest—its long axis is directed from above downward and from right to left. But instead of lying to the left of the sternum, it is located to the right of the median line of the body. Carefully studied cases of dextrocardia of this type have been reported by Bard,[14] Galliard,[15] Lortat-Jacob and Laignel-Lavastine,[16] Barbier[17] and many others. I encounter these cases comparatively often and at the Montefiore Home I have had four under observation during the last three years. They are very rare in acute cases, running speedily to termination by death, but in those which run a chronic course extending over many years, dextrocardia may occur in extensive right-sided lesions. They also occur in cases of pleurisy which are strongly adhesive from the beginning, and follow rapid absorption of a pleural exudate when the lung does not reexpand quickly to fill up the space left vacant by the disappearance of the fluid. In these cases the pleura forms a thick shell around the collapsed lung into which it sends forth thick fibrous bands. When the latter contract they may drag the mediastinum, thus filling up vacant space in the right hemithorax.

I want to say a few words about those rare cases of dextrocardia in which the base of the heart remains in nearly its normal position, while the apex is found in the right mammillary line, or even further toward the axilla; the direction of its long axis is from above downward and from left to right. It was this sort of case of dextrocardia that formerly led to the belief that in some dextrocardias the heart is swung over to the right side. As has already been stated, such dextrocardias do not exist because the kinking of the great vessels would promptly extinguish life. These forms of dextrocardia usually occur in the following manner: An effusion into the left pleura pushes the entire mediastinum to the right and keeps it there until the fluid is absorbed or removed. In the vast majority of cases the heart then returns to its normal location

15. Galliard, M. L.: Dextrocardie par attraction, Bull. et mém. Soc. méd. d. hôp. de Paris, 1908, xxv, 634.

16. Lortat-Jacob and Laignel-Lavastine: Dextrocardie acquise par retraction pleuro-pulmonaire avec caverne tuberculeuse, Bull. et mem. Soc. méd. d. hôp. de Paris, 1906, xxiii, 814.

17. Barbier: Un cas de dextrocardie au cours d'une sclerose pulmonaire tuberculose droite, Bull. et. mém. Soc. d. hôp. de Paris, 1900, xxvii, 187.

on the left side; but in some rare cases in which the right pleura is affected, the apex of the heart, while sojourning in the right hemithorax, is bound down by strong pleuropericardial adhesions, so that while the base, which is free, moves back to its normal place, the apex remains fixed in its abnormal position. Such a case has been reported in detail by Chalier and Rebattu,[18] and in one case that I have seen this was the only plausible explanation for the anomalous position of the heart.

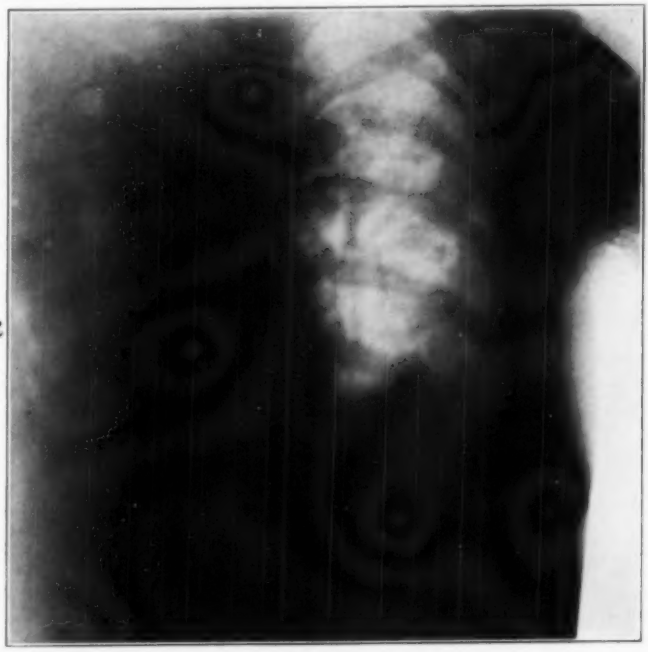

Fig. 6.—Acquired dextrocardia.

While in most cases of cardiac dislocation in tuberculosis the heart is displaced toward the affected side and in bilateral lesions to the side in which the older and more serious lesion is found, there are many exceptions. Pleuropericardial adhesions often prevent dislocation of the heart, which ordinarily would be pulled or pushed out of place. At times we encounter extensive infiltration, or a large cavity in the right upper or middle lobe, while the heart is dislocated 1 or 2 inches to the left. In these anomalous cases I almost invariably found that in addi-

18. Chalier, J., and Rebattu, J.: Des dextrocardies acquises, Paris méd., 1912, p. 365.

tion to the lesion in the right lung, there was also a thickened pleura at the left base, adherent to the left side of the pericardium which pulled and fixed the heart toward the left side.

The routine methods of physicial exploration show the location of the displaced heart in phthisis easily and vividly; but in many cases the diagnosis is very difficult, and occasionally almost impossible. The side of the heart adjoining the healthy lung is easily made out by percussion, but the cardiac dulness at the side adjoining the affected lung merges with the dulness of the infiltrated and consolidated lung-tissue or thickened pleura, and is difficult to separate by any method of percussion. The fluoroscope and the roentgenographic plate also fail at times to show a definite outline of the borders between the heart and lung. Indeed, I have found in many cases that the orthodiascope was of no value, because extensive infiltration and thickened pleura have obscured all outlines which in normal subjects show such a clear picture of the heart and lungs. The diagnosis of dextrocardia is also sometimes difficult. Of course, from complete transposition of the viscera it is easily distinguished when the location of the liver, spleen, etc., is noted; but when we find the heart on the right side, the apex beating to the right of the sternum and the liver, spleen, etc., in their normal locations, the question may arise whether we are not dealing with one of those rare cases of congenital transposition of the heart in which this is the only organ displaced. This is especially true of cases in which the heart was dislocated by a latent pleurisy during infancy of which the patient can give no account. The electrocardiograph may give us positive information in these cases, as by a study of the records from the different leads the axis of the heart may readily be determined. We had a case at the Montefiore Home in which the question arose whether it was congenital or acquired, and the Roentgen ray could give no positive diagnostic clues. The electrocardiogram taken by Dr. B. S. Oppenheimer, however, showed a normal tracing.

While percussing and auscultating these chests, it is to be borne in mind that the heart is not only shifted from left to right, but in many cases there is also some rotation of that organ on its vertical or sagittal axis—the base approaching the chest wall, while the apex is shifted away from it. As a result it often happens that the point at which the impulse of the apex is apparently found is altogether the impulse of the right ventricle. Occasionally we find two points with impulse beneath—one in the second or third right intercostal space, and another near the xyphoid cartilage. As a general rule, we may say that when on inspection palpation and auscultation we find the heart-beat at only one point, it is the base or the right ventricle which is visible and palpable, because in these cases the apex is turned away from the anterior

chest wall; when two points are found with impulses, the one to the left represents the apex and the one to the right represents the base for reasons just made clear.

Even in moderate dislocations we find that the cardiac sounds undergo important modifications. While it is undoubtedly true that the great frequency of the accentuation of the second pulmonic sound, as well as the impulse at the second left intercostal space near the sternum, are due to pulmonary retraction, yet in a large number of cases the dislocation of the heart and rotation on its vertical axis are responsible for it

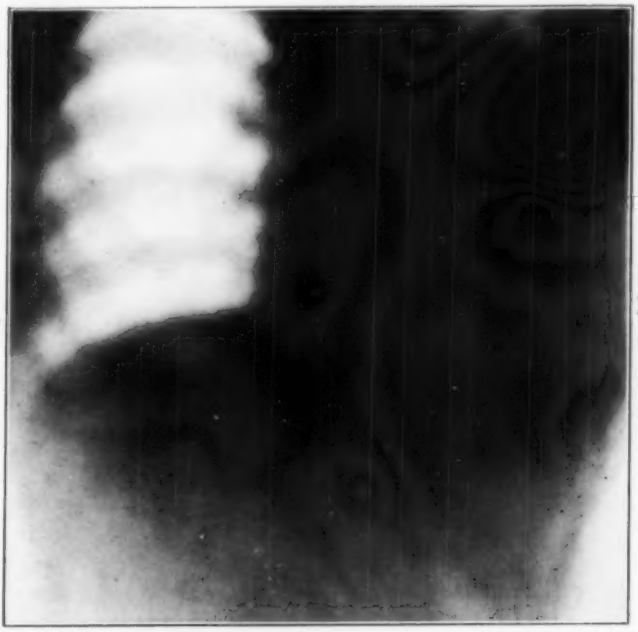

Fig. 7.—Acquired dextrocardia; large cavity in right upper and middle lobes; thickened right pleura; vicarious emphysema of left lung.

in a great measure. Similarly, often no apex-beat can be seen or felt, although percussion and auscultation show that it is located in its normal place. In some this is due to an emphysematous lung covering the apex, but in others rotation with shifting backward is responsible. At times we find that although the apex is shifted to the left, the cardiac impulse remains within the mammillary line, which is also due to rotation of the heart on its vertical or sagittal axis. The fact is that two cases of cardiac dislocation showing the same signs and symptoms are very rare, which is clear when we bear in mind the various directions

in which traction by fibrous bands may be exerted and the different locations of shrinking pulmonary tissue, cavitation, compensatory emphysema, as well as the condition of the pleura in its relation to the pericardium, and above all the position of the diaphragm. It has been my impression that in displacements to the left, the second pulmonic sound is very frequently accentuated, while dislocations to the right are more often accompanied by an accentuation of the aortic sounds. In both cases it may be due to either greater conductivity of densely infiltrated lung tissue, to obstruction of the pulmonary circulation as in emphysema, or to the fact that the base of the heart has been moved nearer to the anterior chest wall.

The effects of cardiac dislocations on the circulation and on the general condition of the patient depend on several factors, especially the rapidity with which it is accomplished, the distance it is dislocated out of its normal position, and also the mode of displacement. Most dislocations are found in very old and chronic cases, mainly in fibroid phthisis, and the effects on the circulation come on slowly and insidiously, the heart adapting itself more or less to its new position. Pottenger[3] observed a case in which the heart moved more than 1 inch to the right within a few days' time owing to the formation of a large cavity in the right lung near the heart border. The symptoms were extreme weakness, dyspnea, rapid heart-action and a tendency to syncope, loss of appetite and nausea, especially when the patient changed his position. In a case under my care, the heart was dislocated upward and to the left about 1½ inches out of place within two weeks, and the patient, a boy aged 15, suffered from extreme prostration, dyspnea and tachycardia, and also showed signs of cerebral anemia.

In all the chronic cases of tuberculosis in which the heart is appreciably dislocated, tachycardia is a constant symptom; but tachycardia is a cardinal symptom of phthisis without cardiac displacement, and has been attributed by various authors to pressure on the vagus by swollen bronchial glands, or fibrous scars, etc., and also to the toxemia of the disease. In cardiac dislocation, however, we have an added mechanical factor. In my experience annoying tachycardia is extremely rare in afebrile cases of phthisis, unless there is also cardiac dislocation, when it becomes an important symptom, and the least exertion results in severe palpitation, dyspnea, weakness, etc. Ruedinger believes that there are undoubtedly forms of tuberculosis in which the rapid heart-action is primarily due to disturbances in the mechanism of the heart as a result of the dislocation. When we examine these cases fluoroscopically, we find obvious reasons for cardiac embarrassment in the displacement of the thoracic organs. Some healed cases of tuberculosis

remain permanently with tachycardia, and inasmuch as toxemia cannot be held responsible for the rapid heart-action in inactive cases, the dislocation of the heart may be held accountable.

SUMMARY AND CONCLUSIONS

Cardiac dislocations are very frequently found in pulmonary tuberculosis. In far-advanced cases of phthisis it is exceptional to find the heart in its normal location, over 75 per cent. of cases showing displacements of the heart. In moderately advanced cases between one-third and one-half show displacements, and even some early cases are thus affected.

The dislocation is usually produced by traction exerted from the affected side. Pulmonary collapse and retraction, cavitation and fibrous bands running from the pleura to the pericardium drag the heart out of its normal place. Pressure exerted by a vicariously emphysematous lung on the opposite side greatly assists in displacing the heart to the affected side, or, in bilateral lesions, to the side which has the older or more serious lesion. In many cases we can determine in which side the tuberculous lesion is located, or in bilateral lesions in which side the older or more extensive lesion is located, by determining the location of the heart.

Dislocations take place more often toward the left hemithorax than toward the right for various anatomical reasons, mainly, however, because of the oblique position of the heart from right to left, and the strong attachment of the mediastinum to the central tendon of the diaphragm, which greatly counteracts traction exerted from the right pleura and lung. As a result we find that about two-thirds of all displacements are toward the left side. In far-advanced cases the displacements are about equal between the two sides of the chest, and dextrocardia is not uncommon. Acquired dextrocardia is almost invariably of tuberculous origin.

In many cases of phthisis the heart is not only dislocated, but also rotated on its sagittal or vertical axis. In the normal position the cardiac apex is nearer the chest wall than the base. Traction exerted on the right side of the mediastinum may bring the base of the heart nearer the chest wall and push or pull the apex away from it. Elevation of the diaphragm also has a great influence on the position of the heart, and together with pleuropericardial adhesions may dislocate the heart in any manner—upward, downward, to the right or left; may bring it in a horizontal or vertical position, etc.

In the majority of cases the diagnosis of displacement can be made by percussion, auscultation and roentgenoscopy; but in some cases only the side of the heart adjoining the healthy lung can be mapped out by percussion, while on the opposite side its dulness merges with that of the pulmonary or pleural lesion and cannot be differentiated easily, and at

times even the Roentgen ray is of no avail. In dextrocardia a good guide is the cardiac impulse. When we find only one point with an impulse, it is usually the right ventricle that pulsates and not the apex, because in these cases the latter is turned away from the anterior chest wall; if we find two points with pulsation, the one to the left represents the apex and the one to the right the base or the right ventricle.

While tachycardia and dyspnea of phthisis are usually due to toxemia of the disease, the cardiac displacements are also responsible to some extent. Many patients cured of tuberculosis remain with permanent cardiac embarrassment because of the displacement of the heart.

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